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The TetR Family of Regulators

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SUMMARY

The most common prokaryotic signal transduction mechanisms are the one-component systems in which a single polypeptide contains both a sensory domain and a DNA-binding domain. Among the >20 classes of one-component systems, the TetR family of regulators (TFRs) are widely associated with antibiotic resistance and the regulation of genes encoding small-molecule exporters. However, TFRs play a much broader role, controlling genes involved in metabolism, antibiotic production, quorum sensing, and many other aspects of prokaryotic physiology. There are several well-established model systems for understanding these important proteins, and structural studies have begun to unveil the mechanisms by which they bind DNA and recognize small-molecule ligands. The sequences for more than 200,000 TFRs are available in the public databases, and genomics studies are identifying their target genes. Three-dimensional structures have been solved for close to 200 TFRs. Comparison of these structures reveals a common overall architecture of nine conserved α helices. The most important open question concerning TFR biology is the nature and diversity of their ligands and how these relate to the biochemical processes under their control.

INTRODUCTION

Prokaryotes use signal transduction systems to sense alterations in the environment and respond accordingly. These signal transduction systems can be broadly divided into two categories: one-component systems and two-component systems (1, 2). In one-component systems, the sensory and output functions are located on the same polypeptide, while in two-component sys-

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TABLE 1 Major families of one-component signal transduction systems

One-component system	Defining features	Reference(s)
AraC/XlyS	Involved in regulating pathways for the catabolism of various sugars, primarily transcriptional activators, C-terminal DNA-binding domain	196
ArgR	Involved in regulating amino acid metabolism, typically function as transcriptional repressors, N-terminal DNA-binding domain	197
ArsR/SmtB	Involved in regulating metal homeostasis, primarily transcriptional repressors, DNA-binding domain located near the center of the protein	198
AsnC/Lrp	Involved in regulating amino acid metabolism, function as both transcriptional activators and repressors, N-terminal DNA-binding domain	199
Crp/Fnr	Involved in regulating many cellular processes, may function as activators and repressors, C-terminal DNA-binding domain	200
DeoR	Involved in regulating sugar metabolism, typically function as repressors, N-terminal DNA-binding domain	201
DtxR	Involved in regulating metal homeostasis, primarily transcriptional repressors, N-terminal DNA-binding domain	202
Fur	Involved in regulating metal homeostasis, primarily transcriptional repressors, N-terminal DNA-binding domain	202
GntR	Involved in regulating numerous cellular processes, typically function as transcriptional repressors, N-terminal DNA-binding domain	203
IclR	Involved in regulating carbon metabolism, function as both transcriptional activators and repressors, N-terminal DNA-binding domain	204
LacI	Involved in regulating carbon metabolism, typically function as transcriptional repressors, N-terminal DNA-binding domain	205
LuxR	Involved in regulating quorum sensing, typically function as activators, C-terminal DNA-binding domain	206
LysR	Involved in regulating many cellular processes, function as both activators and repressors, N-terminal DNA-binding domain	207
MarR	Involved in regulating antibiotic resistance, typically function as transcriptional repressors, DNA-binding domain located near the center of the protein	208
MerR	Involved in regulating metal homeostasis, typically function as transcriptional repressors, N-terminal DNA-binding domain	209
MetJ	Involved in regulating many cellular processes, typically function as transcriptional repressors, N-terminal DNA-binding domain	3
ModE	Involved in regulating metal homeostasis, function as both transcriptional activators and repressors, N-terminal DNA-binding domain	210
PadR	Poorly characterized family, N-terminal DNA-binding domain	211
TetR	Involved in regulating antibiotic resistance, typically function as repressors, N-terminal DNA-binding domain	14
Xre	Involved in regulating various cellular processes, typically function as transcriptional repressors, N-terminal DNA-binding domain	212, 213

tems, the sensory and output functions are located on separate polypeptides. While the term two-component system is better known, one-component systems are actually much more abundant in prokaryotes (2). There are at least 20 families of prokaryotic one-component systems that can be defined by amino acid conservation in their DNA-binding domains and are defined by different conserved motifs (e.g., pfam and Interpro) (Table 1). The majority of one-component systems employ a helix-turn-helix DNA-binding domain, the exception being transcription factors of the MetJ family, which instead contain a ribbon-helix-helix domain (3). The DNA-binding domains are typically located at either the N- or C-terminal end of the polypeptide, depending on the particular family, although a few instances where the DNA-binding domain has a more central location are apparent. It has been suggested that there is a correlation between the location of the DNA-binding domain and repressor and activator activity. The suggestion was that repressors generally contain an N-terminal DNA-binding domain, while activators generally contain a C-terminal DNA-binding domain (4, 5). While this may hold true for many transcription factors, we would advise caution because there are well-documented exceptions to this rule (6).

The naming of protein families is characterized by a founder effect of sorts, where the family name is derived from the first characterized member. One-component systems are no exception. This can be misleading, however, as not every member of a particular family is likely to be involved in regulating the same basic process as the founder. For example, many regulators in the AraC family are known for their role in sugar metabolism as AraC itself regulates genes required for arabinose catabolism (7). However, some members of the family recognize small molecules other than sugars and play a role in the regulation of virulence, morphological development and antibiotic production (8–10). In fact, some AraC family regulators (e.g., MarA and SoxS) are believed to lack a ligand-binding domain and may not serve as one-component signaling systems at all. Similar to the case for AraC family regulators, not all ArsR or MerR homologs bind metals like the founding member of the family. ArsR homologs have been identified as part of toxin-antitoxin systems (11), and MerR homologs are now known to respond to various chemical stressors (12).

The TetR family of regulators (TFRs) is a large and important family of one-component signal transduction systems (13, 14). While members of this family are best known for their roles as regulators of antibiotic efflux pumps, this in fact describes a minority of their functional roles. Indeed, characterized members are known to regulate numerous aspects of bacterial physiology and to interact with a vast array of ligands (Fig. 1).

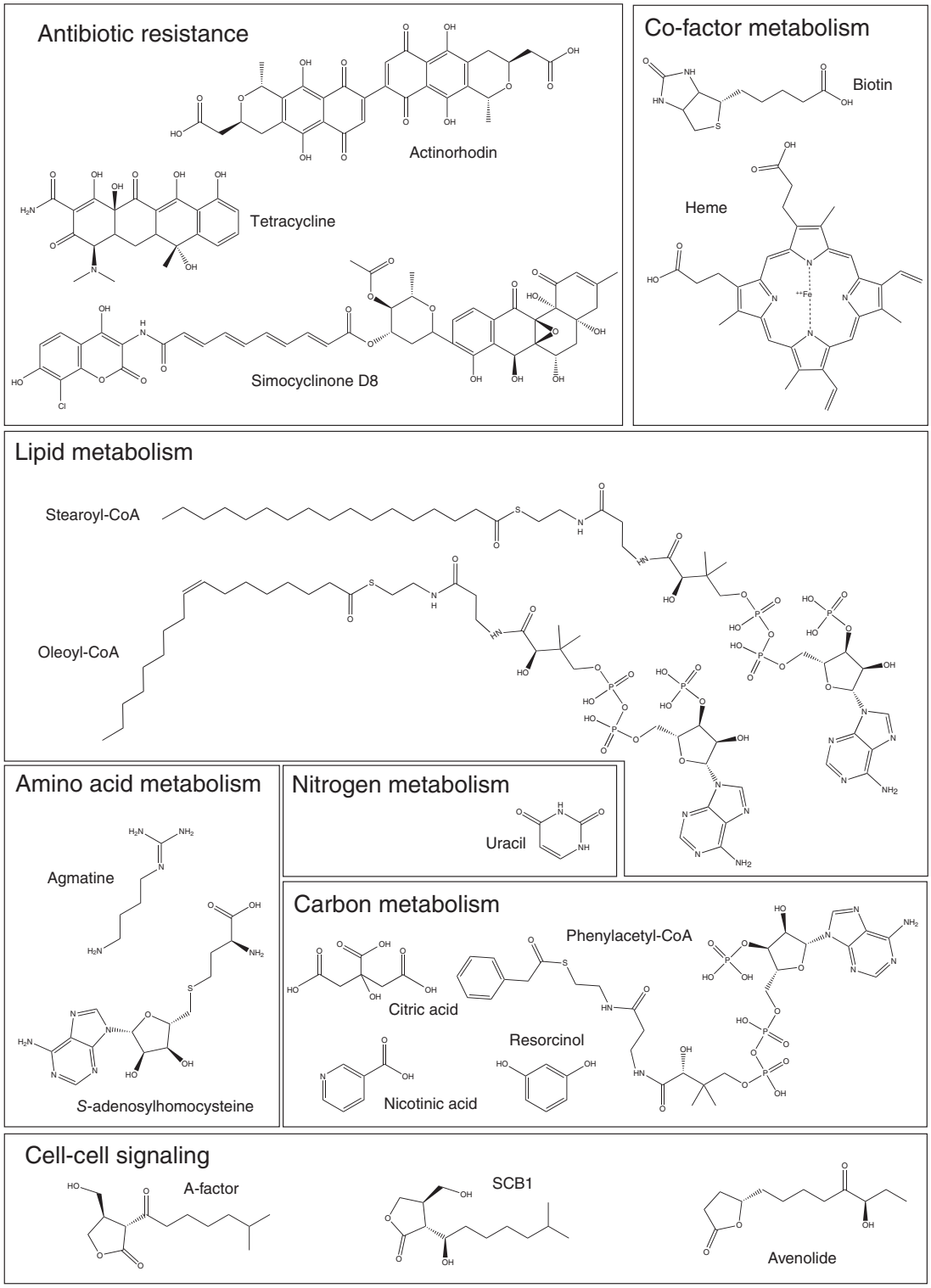

FIG 1 TFRs are known to interact with an exceptionally diverse set of small molecules, including antibiotics, metabolites, and cell-cell signaling molecules.

TetR FAMILY REGULATORS

All TetR family regulators (TFRs) consist of an N-terminal DNA-binding domain and a larger C-terminal domain. The proteins are almost exclusively α helical and function as dimers. In most cases the C-terminal domains interact with one or more ligands, in turn altering the regulator's ability to bind DNA. The exceptional diversity of these ligands is a chief source of interest in these regulators and is a central focus in this review. The name "TFR" is derived from the TetR protein, which was the first family member to be discovered and characterized in detail. Like TetR, many TFRs

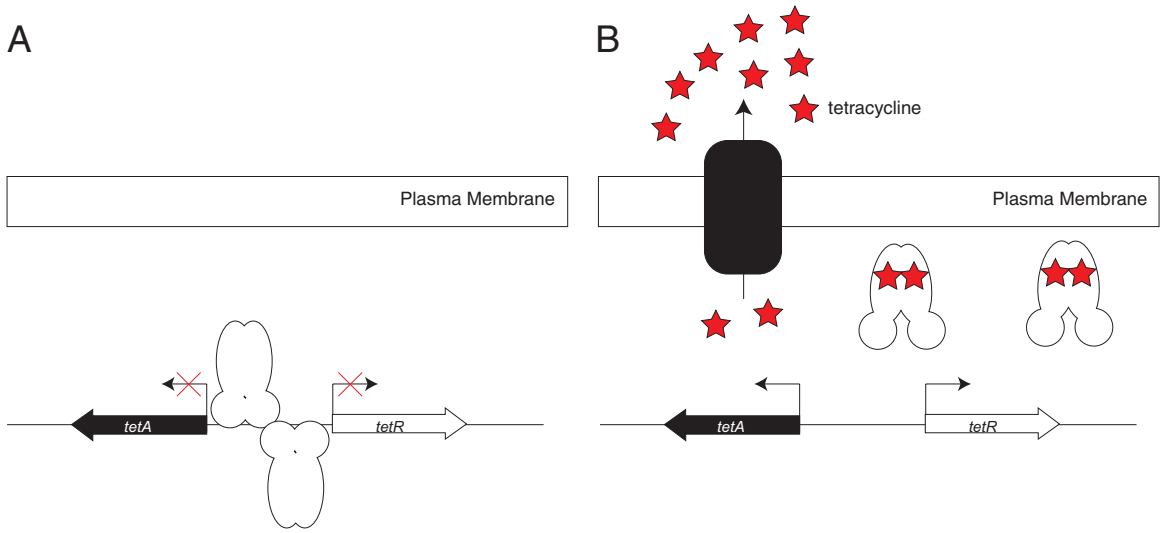

FIG 2 TetR regulates the expression of the tetracycline resistance determinant encoded by *tetA*. (A) In the absence of tetracycline, a pair of TetR dimers bind to repeated palindromic sequences in the intergenic region between *tetR* and *tetA*. (B) When present, tetracycline is bound by TetR, causing a conformational change such that TetR can no longer bind DNA. This allows for expression of the tetracycline efflux pump encoded by *tetA*.

are repressors; however, there are important exceptions that are activators or that have roles unrelated to transcription.

The inducible nature of tetracycline resistance in *Escherichia coli* was recognized in the mid-1960s (15). The protein factor responsible for the regulation and induction of tetracycline resistance, which we now know as TetR, was partially purified a decade later (16). The sequence of *tetR* and many of the molecular details surrounding the regulation of tetracycline resistance were unraveled in the 1980s (17–21). We now know that TetR is the repressor of the tetracycline efflux pump encoded by *tetA* (Fig. 2). In the absence of tetracycline, a pair of TetR dimers bind to overlapping operator sequences in the intergenic region between the divergently transcribed *tetR* and *tetA* genes. When tetracycline is present, it binds directly to TetR, trapping it in a conformation that is incompatible with DNA binding (22). This allows transcription of both *tetR* and *tetA*.

More than 240 TFRs have been at least partially characterized (Table 2), and while TetR remains one of the central models for the family, it is clear that TetR does not represent the enormous diversity seen in the family. Its well-documented role as a regulator of antibiotic efflux is shared by at most 25% of the TFR family members (23). We know that other TFRs function as both repressors and activators (e.g., DhaS), serve as local or global regulators (e.g., AmtR), and can interact with small-molecule or protein ligands (e.g., SlmA). TFRs can be autoregulatory, can be under the control of other transcription factors (e.g., AtrA), or may undergo posttranscriptional regulation (e.g., HapR). In spite of many years of investigation, central questions remain unanswered. For example, while the repressing (i.e., DNA-bound) and induced (i.e., ligand-bound) conformations of TetR have been described in detail, the manner in which the protein converts from one form to the other has not. Furthermore, it is unlikely that the conformational transitions of TetR describe those of all other TFRs, and indeed, the structure of TetR is atypical for the family as a whole (24). It is unclear whether there are distinct conformational subgroups within the family or whether each protein is in fact unique. More globally, in the vast majority of cases, the ligand(s) bound by TFRs have yet to be identified. In this review we discuss what we can learn about TFRs from genomics and structural studies and how this informs, and is informed by, the roles attributed to TFRs in bacterial physiology through more detail-oriented molecular genetic investigation. We incorporate phylogenomics as a new means of organizing TFRs.

GENOMICS OF TFRs

A text-based search for TetR in the NCBI protein database gives well over 200,000 hits (as of 7 March 2013), and this number will continue to grow due to the explosion of whole-genome sequences available. The N-terminal DNA-binding domain of TFR family members is represented by conserved motifs or profiles in the public databases (e.g., IPR001647, PS50977, and pfam00440) and has been defined in previous reviews (14), aiding in the identification of TFRs from whole-genome sequences. While the vast majority of these TFRs have not been characterized, the availability of genome sequences allows us to examine different aspects of the genomics of TFRs.

Distribution of TFRs in Bacterial Genomes

Most sequenced bacterial genomes encode at least one TFR (14, 25). In the over 200 genomes that we examined, 23, from 8 genera, did not encode TFRs. TFRs were not found in at least some representatives from *Borrelia*, *Chlamydia*, *Chlamydophila*, *Francisella*, *Helicobacter*, *Mycoplasma*, *Prosthecochloris*, and *Treponema*. These are predominantly pathogens with genomes under 2 Mbp in size. In contrast, the *Actinobacteria*, along with other soil-dwelling isolates such as *Burkholderia*, *Pseudomonas*, and *Rhizobium* strains, encode the highest numbers of TFRs. *Amycolatopsis* (formerly *Streptomyces*) sp. strain AA4 encodes the greatest number of TFRs of the genomes we examined, at 212. Bacteria with large genomes tend to encode more TFRs (Fig. 3) (25). While in some instances this may be a function of the fact that bacteria with large genomes tend to encode a higher number of regulatory proteins, in other instances the situation may be more complex and indicate a preference for TFRs over other families of regulators. For exam-

TABLE 2 TFRs of known function

TFR	Organism	Description[a]	Known ligand(s)	PDB ID	Reference(s)
AbyC	*Verrucosispora maris* AB-18-032	Located in the abyssomicin biosynthesis cluster; predicted to regulate *abyD* encoding a MFS export pump; mutation decreases abyssomicin synthesis			214
AcmG5	*Streptomyces iakyrus*	Located in the actinomycin G biosynthesis cluster			215
AcmP	*Streptomyces chrysomallus* ATCC 11523	Located in the actinomycin D biosynthesis cluster			94
AcmU	*Streptomyces chrysomallus* ATCC 11523	Located in the actinomycin D biosynthesis cluster			94
AcnR	*Corynebacterium glutamicum*	Regulates the aconitase (*acn*) gene		4AC6, 4ACI, 4AF5	145
AcrR	*Escherichia coli*	Regulator of the AcrAB multidrug efflux pump	Rhodamine 6G, ethidium, proflavine	3BCG, 3LHQ, 2QOP	112, 116
AcrR-like	*Escherichia coli*, *Streptococcus uberis*	Putative regulator of *rdmC* and *mph*(*B*) genes involved in spiramycin and tylosin resistance			103, 216
ActR (SCO5082)	*Streptomyces coelicolor*	Located in the actinorhodin biosynthesis cluster; regulates expression of the ActA and ActB efflux pumps	Actinorhodin, (*S*)-DNPA	2OPT, 3B6C, 3B6A	79
AcuR	*Alcaligenes faecalis*	Putative repressor for genes involved in dimethylsulfoniopropionate and acrylate catabolism			217
AcuR	*Rhodobacter sphaeroides*	Regulates expression of AcuI and DddL involved in dimethylsulfoniopropionate and acrylate catabolism	Acrylate		218
AdeN	*Acinetobacter baumannii*	Regulator of the AdeIJK efflux pump			219
AefR	*Pseudomonas syringae*	Regulates AHL production and is required for plant colonization		3CDL	40
AguR	*Pseudomonas aeruginosa* PAO1	Regulates AguBA required for agmatine utilization	Agmatine		181
AlnR2	*Streptomyces* sp. strain CM020	Located in the alnumycin biosynthesis cluster			220
AlpW	*Streptomyces ambofaciens*	Located in the alpomycin biosynthesis cluster and involved in the regulation of kinamycin biosynthesis; similar to gamma-butyrolactone receptors			221
AlpZ	*Streptomyces ambofaciens*	Located in the alpomycin biosynthesis cluster; similar to gamma-butyrolactone receptors			222
AmeR	*Agrobacterium tumefaciens*	Regulates the tripartite RND exporter AmeABC			223
AmiP	*Streptomyces vinaceus-drappus*	Located in the amicetin biosynthesis cluster			95
AmtR	*Corynebacterium glutamicum*	Global regulator of nitrogen control metabolism	GlnK		37
Ang8	*Streptomyces* sp. strain W007	Located in an angucyclinone biosynthesis cluster			224
ArpA	*Streptomyces griseus*	Involved in the regulation of antibiotic production and sporulation	A-factor (GBL)		225
ArpR	*Pseudomonas putida S12*	Regulates the ArpABC efflux pump involved in the export of multiple antibiotics			226
Asm2	*Actinosynnema pretiosum*	Located in the ansamitocin biosynthesis cluster and involved in the regulation of ansamitocin biosynthesis			227
Asm29	*Actinosynnema pretiosum*	Located in the ansamitocin biosynthesis cluster and involved in the regulation of ansamitocin biosynthesis			227
AtrA	*Streptomyces coelicolor*	Pleiotropic regulator of antibiotic biosynthesis			6
AtuR	*Pseudomonas aeruginosa*	Regulates genes required for acyclic terpene utilization			174
Aur1B	*Streptomyces aureofaciens* CCM 3239	Located in the auricin biosynthesis cluster			228
Aur1R	*Streptomyces aureofaciens* CCM 3239	Located in the auricin biosynthesis cluster; similar to gamma-butyrolactone receptors			229
AvaR1	*Streptomyces avermitilis*	Regulator of avermectin biosynthesis; similar to gamma-butyrolactone receptors	Avenolide		127
AvaR2	*Streptomyces avermitilis*	Similar to gamma-butyrolactone receptors			230
AvaR3	*Streptomyces avermitilis*	Pleiotropic regulator of antibiotic production; similar to gamma-butyrolactone receptors			230
AveI	*Streptomyces avermitilis*	Ortholog of AtrA; regulator of antibiotic production			231
Azi42	*Streptomyces sahachiroi*	Located adjacent to the azinomycin B biosynthetic gene cluster; thought to be beyond the boundaries of the cluster			232
BarA	*Streptomyces virginiae*	Involved in the regulation of virginiamycin; similar to gamma-butyrolactone-binding proteins	Virginiae butanolide (GBL)		233
BarB	*Streptomyces virginiae*	Involved in the regulation of virginiamycin; similar to gamma-butyrolactone-binding proteins			234
BarZ	*Streptomyces virginiae*	Located in the virginiamycin biosynthesis cluster; similar to gamma-butyrolactone-binding proteins			235
BdcR (YjgJ)	*Escherichia coli*	Regulator of BdcA expression			28
BecM	*Streptomyces* sp. strain DSM 21069	Located in the biosynthesis cluster for macrolactam BE-14106 biosynthesis			236

BepR	*Brucella suis*	Regulator of the BepDE efflux pump	Deoxycholate		237
BetI	*Escherichia coli*	Regulates expression of BetT, BetA, and BetB required for the synthesis of glycine betaine from choline	Choline		238
BioQ	*Corynebacterium glutamicum* ATCC 13032	Regulates biotin biosynthesis and import			189
BpeR	*Burkholderia pseudomallei*	Regulates the BpeAB-OprB multidrug efflux pump			239
BreR	*Vibrio cholerae*	Regulates the BreAB efflux pump in response to bile	Deoxycholate		39
Brp	*Streptomyces clavuligerus*	Gamma-butyrolactone receptor involved in the regulation of clavulanic acid and cephamycin C biosynthesis			240
BrtA	*Listeria monocytogenes*	Regulator of the MdrT efflux pump	Cholate		241
BspR	*Burkholderia pseudomallei*	Involved in regulating type III secretion systems			242
BtrR1	*Bacillus circulans*	Located in the butirosin biosynthesis cluster and involved in regulation			243
CalR1	*Micromonospora echinospora*	Located in the calicheamicin biosynthesis cluster			244
CampR	*Rhodococcus* sp. strain NCIMB 9784	Divergent to *camK* (6-oxocamphor hydrolase)			177
CamR	*Pseudomonas putida*	Regulator of camphor degradation			245
CasR	*Rhizobium etli*	Regulator of CasA required for colonization and infection of the host			246
CgmR (cg2894, Cgl2612)	*Corynebacterium glutamicum*	Multidrug resistance-related transcription factor	Ethidium bromide, malachite green	2ZOY, 2ZOZ, 2YVH, 2YVE	43, 247
ChlF1	*Streptomyces antibioticus*	Located in the chlorothricin biosynthetic gene cluster			248
ChryX5	*Streptomyces albaduncus*	Located in the chrysomycin biosynthesis cluster; a homolog is not present in the cluster for the related molecule ravidomycin			249
CifR	*Pseudomonas aeruginosa*	Regulator of the Cif toxin	Epibromohydrin		250
CmeR	*Campylobacter jejuni*	Regulator of the CmeABC efflux pump	Taurocholate, cholate, salicylate	2QCO, 3QPS, 3QQA	56
CmtI	*Pseudomonas putida*	Putative regulator of operons required for *p*-cymene/*p*-cumate degradation			175
CmtR	*Pseudomonas putida*	Putative regulator of operons required for *p*-cymene/*p*-cumate degradation			178
ComR	*Escherichia coli*	Regulator of ComC involved in copper permeability	Copper		72
CprA	*Streptomyces coelicolor*	Similar to gamma-butyrolactone receptors; involved in regulating sporulation and antibiotic production			134
CprB	*Streptomyces coelicolor*	Similar to gamma-butyrolactone receptors; involved in regulating sporulation and antibiotic production		1IU5, 1IU6	134
CprS	*Streptomyces coelicolor*	Similar to gamma-butyrolactone receptors			251
CymR	*Pseudomonas putida*	Regulator of the *cym* and *cmt* operons required for *p*-cymene and *p*-cumate degradation	*p*-Cumate		176
DarR (MSMEG_5346)	*Mycobacterium smegmatis*	First cyclic-di-AMP-responsive transcription factor to be identified in bacteria	Cyclic-di-AMP		142
DddH	*Halomonas* sp. strain HTNK1	Putative regulator of genes required for dimethylsulfoniopropionate and acrylate catabolism			252
DesT	*Pseudomonas aeruginosa*	Regulates the expression of the DesCB acyl-CoA desaturase operon	Oleate (corepressor), stearate (inducer)	3LSJ, 3LSR, 3LSP	166
DhaR	*Rhodococcus rhodochrous*	Regulator of haloalkane dehalogenase (DhaA)			143
DhaS	*Lactococcus lactis*	Regulator of the *dha* operon; functions as a transcriptional activator	DhaQ-dihydroxyacetone complex	2IU5	69
EbrR	*Streptomyces lividans*	Regulator of the EbrA efflux pump		3HTJ, 3HTI, 3HTH, 3HTA	253
EbrS	*Streptomyces lividans*	Regulator of the EbrC efflux pump			254
Ecm10	*Streptomyces lasaliensis*	Located in the echinomycin biosynthesis cluster			255
EmhR	*Pseudomonas fluorescens*	Regulates the EmhABC efflux pump that influences production of 2,4-diacetylphloroglucinol and is required for phenanthrene, anthracene, and fluoranthene efflux			256, 257
EncS	*Streptomyces maritimus*	Located in the enterocin biosynthesis gene cluster			258
EnvR (AcrS)	*Escherichia coli*	Divergent to the AcrEF efflux pump; may function as a switch for the alternative expression of AcrAB and AcrEF efflux pumps			259
EpeR	*Streptomyces clavuligerus*	Controls expression of the EpeA efflux pump			260
EsmT4	*Streptomyces antibioticus* Tu 2706	Located in the esmeraldin biosynthesis cluster			261

(Continued on following page)

TABLE 2 (Continued)

TFR	Organism	Description[a]	Known ligand(s)	PDB ID	Reference(s)
EthR	*Mycobacterium tuberculosis*	Regulator of *ethA* encoding a monooxygenase required for the activation of ethionamide	Hexadecyl octanoate	1T56	58
FabR	*Escherichia coli*	Regulator of genes required for unsaturated fatty acid synthesis	Unsaturated thioesters		165
Fad35R (Rv2506)	*Mycobacterium tuberculosis*	Regulator of Fad35 acyl-CoA synthetase	Palmitoyl-CoA		162
FadR (YsiA)	*Bacillus subtilis*	Regulator of fatty acid catabolism	Long-chain acyl-CoAs	1VIO	161
FadR	*Pseudonocardia autotrophica*	Regulates *fad* genes required for fatty acid degradation			158
FadR	*Thermus thermophilus*	Regulator of genes required for fatty acid degradation	Medium to long (C_{10} to C_{18}) straight-chain fatty acyl-CoAs	3ANG, 3ANP	150
FarA	*Streptomyces* sp. strain FRI-5	Gamma-butyrolactone autoregulator that controls antibiotic production	IM-2 (GBL)		262
FasR	*Corynebacterium glutamicum*	Regulator of *accD1* and *fasA* expression required for lipid synthesis			157
FrrA	*Bradyrhizobium japonicum*	Regulator of the FreABC efflux pump	Genistein, daidzein		263
HapR	*Vibrio cholerae*	Master quorum-sensing regulator		2PBX	264
HemR	*Propionibacterium freudenreichii*	Possible regulator of *hem* gene expression required for the conversion of glutamate to protoheme			190
HlyIIR	*Bacillus cereus*	Regulator of hemolysin II expression			265
HnoR (HdnoR)	*Arthrobacter nicotinovorans*	Repressor of 6-hydroxy-D-nicotine oxidase	6-Hydroxy-D- and 6-hydroxy-L-nicotine		266
HrtR	*Lactococcus lactis*	Regulator of the HrtB-HtrA transporter	Heme	3VP5, 3VP5, 3VOX	191, 46
IcaR	*Staphylococcus epidermidis*	Regulator of the *ica* operon required for biofilm formation		2ZCM, 2ZCN	267
IfeR	*Agrobacterium tumefaciens*	Regulator of the IfeAB efflux pump			268
JadR*	*Streptomyces venezuelae*	Located in the jadomycin biosynthesis cluster			269
JadR2	*Streptomyces venezuelae*	Similar to gamma-butyrolactone receptors; involved in the regulation of jadomycin biosynthesis	Jadomycin and chloramphenicol		133, 270
KanG	*Streptomyces kanamyceticus*	Located near the kanamycin biosynthesis cluster but probably beyond cluster boundaries			271
KijA8	*Actinomadura kijaniata*	Located in the kijanimicin biosynthesis cluster	Kijanimicin		272
KijC5	*Actinomadura kijaniata*	Located in the kijanimicin biosynthesis cluster			272
KijR	*Streptomyces coelicolor*	Regulator of KijX expression and kijanimicin resistance	Kijanimicin, saccharocarcins A and B		25
KinR	*Streptomyces murayamaensis*	Located in the kinamycin biosynthesis cluster			273
KirRII	*Streptomyces collinus*	Located in the kirromycin biosynthesis cluster			274
KsbA	*Kitasatospora setae*	Gamma-butyrolactone receptor protein; involved in regulating bafilomycin biosynthesis	GBLs		275
KstR	*Mycobacterium tuberculosis*	Regulator of lipid metabolism		3MNL	169
KstR2	*Mycobacterium tuberculosis*	Regulator of cholesterol metabolism			170
LanK	*Streptomyces cyanogenus*	Located in the landomycin biosynthetic pathway	Landomycin A and intermediates		78
Lct13	*Streptomyces rishiriensis*	Putative gamma-butyrolactone receptor protein; located in the lactonamycin biosynthesis cluster			276
Lct14	*Streptomyces rishiriensis*	Putative gamma-butyrolactone receptor protein; located in the lactonamycin biosynthesis cluster			276
LfrR	*Mycobacterium smegmatis*	Regulator of LfrA multidrug efflux pump	Proflavine	2WGB, 2V57	55
LitR	*Vibrio fischeri*	Involved in regulating luminescence and symbiotic light organ colonization			277
LiuQ (Bamb_4589)	*Burkholderia ambifaria* AMMD	Regulator of branched-chain amino acid degradation			183
LmrA	*Bacillus subtilis*	Regulator of the LmrB efflux pump	Flavonoids (quercetin, fisetin, galangin, catechin, coumestrol, genistein)		104
LplR	*Rhodococcus erythropolis*	Regulator of L-pantoyl lactone dehydrogenase gene expression			278
LuxR	*Vibrio harveyi*	Global regulator			279
LuxT	*Vibrio harveyi*	Global regulator			280
McbR	*Corynebacterium glutamicum*	Global regulator of L-methionine and L-cysteine biosynthesis	*S*-Adenosylhomocysteine		185
Mce3R	*Mycobacterium tuberculosis*	Putative regulator of lipid metabolism			281
MdoR	*Mycobacterium* sp. strain JC1	Regulator of genes required for methanol oxidation			147
MedORF28	*Streptomyces* sp. strain AM-7161	Located in the medermycin biosynthesis cluster			282
MepR	*Pseudomonas putida*	Regulates efflux pump involved in toluene resistance			283

MerO	*Streptomyces* sp. strain NRRL 30748	Located in the meridamycin biosynthesis cluster			284
MexL	*Pseudomonas aeruginosa*	Regulator of the MexJK efflux pump			285
MexZ (AmrR)	*Pseudomonas aeruginosa*	Regulates the MexXY (AmrAB) exporter involved in aminoglycoside resistance		2WUI	286
MlaM	*Streptomyces* sp. strain MP39-85	Located in the biosynthetic gene cluster for the macrocyclic lactam ML-449			92
MmfR	*Streptomyces coelicolor*	Gamma-butyrolactone-like receptor involved in regulating methylenomycin production			128, 287
MmyR	*Streptomyces coelicolor*	Gamma-butyrolactone-like receptor involved in regulating methylenomycin production			128, 287
MmyR	*Streptomyces violaceoruber*	Located in the methylenomycin biosynthesis cluster			288
MnbR	*Comamonas* sp. strain JS46	Putative regulator of *mnb* operon required for 3-nitrobenzoate oxidation			144
MonRII	*Streptomyces cinnamonensis*	Located in the monensin biosynthesis locus			289
MphR	*Escherichia coli*	Regulator of macrolide resistance	14-membered macrolides (erythromycin, oleandomycin)	3G56, 3FRQ	101
MSMEG_6564	*Mycobacterium smegmatis*	Global regulator of DNA repair genes			290
MtrR	*Neisseria gonorrhoeae*	Regulator of the *mtr* efflux pump		3VIB	291
NalC	*Pseudomonas aeruginosa*	Indirect regulator of the MexAB-OprM efflux pump through regulation of ArmR expression	Chlorinated phenols		292, 293, 294, 295
NalD	*Pseudomonas aeruginosa*	Regulator of the MexAB-OprM efflux pump			296
NapR3	*Streptomyces aculeolatus*	Located in the napyradiomycin biosynthesis cluster			297
NapR7	*Streptomyces aculeolatus*	Located in the napyradiomycin biosynthesis cluster			297
NcsR2	*Streptomyces carzinostaticus*	Gamma-butyrolactone receptor located in the neocarzinostatin biosynthesis cluster			298
NcsR3	*Streptomyces carzinostaticus*	Gamma-butyrolactone receptor located in the neocarzinostatin biosynthesis cluster			298
NcsR4	*Streptomyces carzinostaticus*	Located in the neocarzinostatin biosynthesis cluster			298
NemR (YdhM)	*Escherichia coli*	Regulator of *N*-ethylmaleimide reductase	*N*-Ethylmaleimide and other Cys modification reagents		299
NfxB	*Pseudomonas aeruginosa*	Regulator of the MexCD-OprJ efflux pump			300
NicS	*Pseudomonas putida*	Regulator of genes required for nicotinic acid degradation	Nicotinic acid and hydroxynicotinic acid		148
NonG	*Streptomyces griseus*	Located near the nonactin biosynthesis cluster but probably beyond cluster boundaries			301
OpaR	*Vibrio parahaemolyticus*	Global regulator			301
ORF20p	*Streptomyces hygroscopicus*	Located in the geldanamycin biosynthesis locus			
OrfH2	*Streptomyces griseoruber*	Located in the hedamycin biosynthesis locus			302
OvmY	*Streptomyces antibioticus*	Located in the oviedomycin biosynthesis cluster			303
PaaR	*Azoarcus evansii*	Regulator of genes required for phenyl acetic acid degradation			304
PaaR	*Thermus thermophilus*	Regulator of genes required for phenyl acetic acid degradation	Phenylacetyl coenzyme A		150
PapR3	*Streptomyces pristinaespiralis*	Located in the pristinamycin biosynthesis cluster; similar to gamma-butyrolactone receptors			305
PapR5	*Streptomyces pristinaespiralis*	Located in the pristinamycin biosynthesis cluster; similar to gamma-butyrolactone receptors			305
PG1181	*Porphyromonas gingivalis*	Expressed in response to NO stress			306
PgaY	*Streptomyces* sp. strain PGA64	Located in the *pga* angucyclinone biosynthesis cluster			307
PhaD	*Pseudomonas putida*	Regulator of genes required for polyhydroxyalkanoate metabolism			167
PhlF	*Pseudomonas fluorescens*	Located in the 2,4-diacetylphloroglucinol biosynthesis cluster	2,4-Diacetylphloroglucinol (inducer), salicylate (corepressor)		75
PhlH	*Pseudomonas fluorescens*	Located in the 2,4-diacetylphloroglucinol biosynthesis cluster			308
PigZ	*Serratia* sp. strain ATCC 39006	Regulator of the ZrpADBC efflux pump			309
Pip (SCO4025)	*Streptomyces coelicolor*	Regulator of the Pep efflux pump	Pristinamycin I		100
PksA	*Bacillus subtilis*	Located in the bacillaene biosynthesis cluster			310
PlaR2	*Streptomyces* sp. strain Tü6071	Located in the phenalinolactone biosynthesis cluster			311
PltZ	*Pseudomonas* sp. strain M18	Located in the pyoluteorin biosynthesis cluster			312

(Continued on following page)

TABLE 2 (Continued)

TFR	Organism	Description[a]	Known ligand(s)	PDB ID	Reference(s)
PmeR (PSPTO_4302)	*Pseudomonas syringae*	Regulator of MexAB-OprM	Flavonoids		313
PqrA (SCO1568)	*Streptomyces coelicolor*	Regulator of the PqrB efflux pump			314
PsbI	*Rhodopseudomonas palustris*	Regulator of *p*-cumate catabolism	*p*-Cumate		179
PsrA	*Pseudomonas aeruginosa*	Regulator of the β-oxidation operon	Long-chain fatty acids	2FBQ	163
PydR	*Pseudomonas putida* KT2440	Regulator of pyrimidine reductive catabolic pathway			154
Pyr27	*Actinosporangium vitaminophilum*	Located in the pyrrolomycin biosynthesis cluster			315
Pyr3	*Actinosporangium vitaminophilum*	Located in the pyrrolomycin biosynthesis cluster			315
PyrO	*Streptomyces pyridomyceticus*	Located in the pyridomycin biosynthesis cluster; similar to gamma-butyrolactone receptors			316
QacR	*Staphylococcus aureus*	Regulator of the QacA efflux pump	Rhodamine 6G, dequalinium, crystal violet, berberine, $DiOC^3$, methyl green, benzalkonium, tetraphenylarsonium, nitidine, palmatine	1JTX, 1JT6, 1JTY, 1JUM, 1JUP, 1JUS, 1JTO, 1QVT, 1QVU	60, 53
QdoR (YxaF)	*Bacillus subtilis*	Regulator of quercetin dioxygenase QdoI (YxaG)	Flavonoids (quercetin, fisetin, tamarixetin, galangin, genistein, coumestrol)		317
RamR (STM0580)	*Salmonella enterica* serovar Typhimurium	Regulator of the RamA efflux pump; mutations in the RamR binding site result in a multidrug resistance phenotype			318
RefZ (YttP)	*Bacillus subtilis*	Involved in the switch from medial to polar cell division			195
RegE	*Actinoplanes friuliensis*	Located in (or adjacent to) the friulimicin biosynthesis cluster			319
RemM	*Streptomyces resistomycificus*	Located in the resistomycin biosynthesis cluster			320
RemQ	*Streptomyces resistomycificus*	Located in the resistomycin biosynthesis cluster			320
RifQ	*Amycolatopsis mediterranei*	Located in the rifamycin biosynthesis cluster			91
RkI	*Streptomyces strain* sp. 88-682	Located in the RK-682 biosynthesis cluster			321
RmiR	*Rhizobium etli*	Regulator of NodTch			322
RmrR	*Rhizobium etli*	Regulator of the RmrAB efflux pump			323
RolR	*Corynebacterium glutamicum*	Regulator of resorcinol degradation	Resorcinol	3AQS, 3AQT	49
RphA3	*Streptomyces griseoviridis*	Located in the prodigiosin biosynthesis cluster			324
RrdA (SCO1104)	*Streptomyces coelicolor*	Regulator of antibiotic production			325
RutR (YcdC)	*Escherichia coli*	Regulator of pyrimidine synthesis	Uracil		326
Rv3066	*Mycobacterium tuberculosis*	Regulator of Mmr multidrug efflux pump	Ethidium	3V6G, 3V78	327
SaaR	*Streptomyces ambofaciens*	Gamma-butyrolactone receptor involved in regulating spiramycin production			328
SabR	*Streptomyces ansochromogenes*	Gamma-butyrolactone receptor involved in regulating nikkomycin production			329
SabR	*Streptomyces acidiscabies*	Gamma-butyrolactone receptor involved in regulating WS5995B production			330
SabS	*Streptomyces acidiscabies*	Gamma-butyrolactone receptor involved in regulating WS5995B production			330
SACE_7040	*Saccharopolyspora erythraea*	Regulator of morphological differentiation			331
SaqK	*Micromonospora* sp. strain Tu 6368	Located in the saquayamycin Z biosynthesis cluster			83
SAV3818	*Streptomyces avermitilis*	Global upregulator of antibiotic production in *Streptomyces* species			332
SbtR	*Thermus thermophilus* HB8	Contains an intermolecular disulfide bridge that may be involved in ligand affinity		3VUQ	333
SCAB1401	*Streptomyces scabies*	Located in the pyochelin biosynthesis cluster			334
ScbR	*Streptomyces coelicolor*	Gamma-butyrolactone-binding protein; pleiotropic regulator of antibiotic production	SCB1		251
ScbR2	*Streptomyces coelicolor*	Similar to gamma-butyrolactone-binding proteins; regulator of Cpk polyketide production and gamma-butyrolactone biosynthesis	Actinorhodin and undecylprodigiosin		131, 132, 133
SchA21	*Streptomyces* sp. strain SCC-2136	Located in the biosynthesis cluster for the angucyclinones Sch 47554 and Sch 47555			335
SchA4	*Streptomyces* sp. strain SCC-2136	Located in the biosynthesis cluster for the angucyclinones Sch 47554 and Sch 47555			335
SchR3	*Streptomyces chartreusis*	Located in the biosynthesis cluster for calcimycin (A23187)			93
SCO0253	*Streptomyces coelicolor*	Regulator of SCO0252	Tetracycline	3FIW	336
SCO0332	*Streptomyces coelicolor*	Regulator of SCO0330		2ZB9	337

SCO1712	*Streptomyces coelicolor*	Regulator of antibiotic production		3BNI	338, 160
SCO3201	*Streptomyces coelicolor*	Regulator of antibiotic production			339
SczA	*Streptococcus pneumoniae*	Regulator of metal ion homeostasis	Zn^{2+}		71
SfmR1	*Streptomyces lavendulae*	Located in the saframycin A biosynthesis cluster			340
SimR	*Streptomyces antibioticus*	Located in the simocyclinone D8 biosynthesis cluster	Simocyclinones D8 and C4	2Y2Z, 2Y30, 2Y31	76
SlgR1	*Streptomyces lydicus*	Located in the streptolydigin biosynthesis cluster			341
SlmA	*Escherichia coli*	Nucleoid occlusion factor	FtsZ	3NXC	192, 193
SmcR	*Vibrio vulnificus*	Global regulator		3KZ9	342, 343
SmeT	*Stenotrophomonas maltophilia*	Regulator of the SmeDEF efflux pump	Triclosan	2W53	52, 61, 344
SMU_1349	*Streptococcus mutans*	Regulator of the TnSmu2 operon, which contains a secondary metabolite biosynthesis gene cluster			345, 346
SngR	*Streptomyces natalensis*	Gamma-butyrolactone receptor protein involved in regulating natamycin biosynthesis and sporulation			347
SocA3	*Myxococcus xanthus*	Involved in regulating morphological development			348
SpbR	*Streptomyces pristinaespiralis*	Gamma-butyrolactone receptor protein involved in regulating pristinamycin biosynthesis and sporulation			349, 305
SrpR	*Pseudomonas putida*	Regulator of the SrpABC efflux pump	SrpS		350, 351
SrrA	*Streptomyces rochei*	Gamma-butyrolactone receptor protein involved in regulating lankacidin and lankamycin biosynthesis and sporulation			352, 353
SrrB	*Streptomyces rochei*	Gamma-butyrolactone receptor protein involved in regulating lankacidin and lankamycin biosynthesis and sporulation			352
SrrC	*Streptomyces rochei*	Gamma-butyrolactone receptor protein involved in regulating lankacidin and lankamycin biosynthesis and sporulation			352
SscR	*Streptomyces scabies*	Gamma-butyrolactone receptor protein involved in regulating secondary metabolism	GBLs		354
SsfT2	*Streptomyces* sp. strain SF2575	Located in the biosynthesis cluster for the polyketide SF2575			99
Strop_2766	*Salinispora tropica*	Located in the salinilactam biosynthesis cluster			355
TamK	*Streptomyces* sp. strain 307-9	Located in the tirandamycin biosynthesis cluster			356
SwrT	*Vibrio parahaemolyticus*	Ortholog of *V. harveyi* LuxT; regulator of swarming motility			357
TarA	*Streptomyces tendae*	Gamma-butyrolactone receptor protein involved in regulating nikkomycin production			358
TcaR2	*Micromonospora chalcea*	Located in the tetrocarcin A biosynthesis cluster			359
TcmR	*Streptomyces glaucescens*	Located in the tetracenomycin C biosynthesis cluster			360
Tei8	*Actinoplanes teichomyceticus*	Located in the teicoplanin biosynthesis cluster			361
TetR	*Escherichia coli*	Regulator of tetracycline resistance	Tetracycline	2TCT, 1QPI	362
TetR	*Arthrobacter oxydans*	Putative regulator of genes required for phenyl acetic acid degradation			363
TetR	*Streptomyces toxytricini*	Putative regulator of the propionyl-CoA carboxylase complex			364
Tmn21	*Streptomyces* sp. strain NRRL 11266	Located in the tetronomycin biosynthesis cluster			365
TR	*Mycobacterium peregrinum*	Putative regulator of macrolide resistance			366
TrdK	*Streptomyces* sp. strain SCSIO1666	Located in the tirandamycin biosynthesis cluster			367
Tsn22	*Streptomyces longisporoflavus*	Located in the tetronasin biosynthesis cluster			GenBank accession no. FJ462704
TtgR	*Pseudomonas putida*	Regulator of the TtgABC efflux pump	Phloretin, naringenin, chloramphenicol, tetracycline, quercetin, luteolin	2UXP, 2UXI, 2UXH, 2UXU, 2UXO	51, 368, 369
TtgW	*Pseudomonas putida*	Divergent to the TtgGHI efflux pump but does not play a major role in regulation			370
TvrR	*Pseudomonas syringae*	Required for pathogenesis			371

(Continued on following page)

TABLE 2 (Continued)

TFR	Organism	Description[a]	Known ligand(s)	PDB ID	Reference(s)
TylP	*Streptomyces fradiae*	Gamma-butyrolactone receptor protein involved in regulating tylosin production and sporulation			372, 373
TylQ	*Streptomyces fradiae*	Gamma-butyrolactone receptor protein involved in regulating tylosin production			373
UidR	*Escherichia coli*	Regulator of the D-glucuronidase UidA			374
UrdK	*Streptomyces fradiae*	Located in the urdamycin biosynthesis cluster			84
VanT	*Vibrio* (*Listonella*) *anguillarum*	Global regulator			375
VarR	*Streptomyces virginiae*	Located in the virginiamycin biosynthesis cluster	Virginiamycin S		77
VceR	*Vibrio cholerae*	Regulator of VceCAB efflux pump	Carbonyl cyanide *m*-chlorophenyl hydrazone		376
VexR	*Vibrio cholerae*	Regulates the VexAB efflux pump which is expressed in response to bile, sodium dodecyl sulfate, or novobiocin			39
VlmE	*Streptomyces viridifaciens*	Located in the valanimycin biosynthesis cluster			377
VtpR	*Vibrio tubiashii*	Global regulator of virulence factors			378
XdhR (SCO1135)	*Streptomyces coelicolor*	Regulator of xanthine dehydrogenase			156

[a] MFS, major facilitator superfamily; AHL, acyl-homoserine lactone.

ple, *Streptomyces coelicolor* encodes 965 regulatory proteins in its approximately 8.7-Mbp genome (26). Of these regulators, 153 (15.8%) are TFRs, while only 34 (3.5%) are AraC family regulators and 40 (4.1%) are LysR family regulators (L. Cuthbertson and J. R. Nodwell, unpublished data). *E. coli* encodes 261 DNA-binding transcription factors in its 4.6-Mbp genome, of which 13 (5.0%) are TFRs, 28 (10.7%) are AraC family regulators, and 46 (17.6%) are LysR family regulators (27). Exceptions where bacteria with large genomes encode a relatively small number of TFRs include some deltaproteobacteria (e.g., *Myxococcus* and *Stigmatella*) and members of the phyla *Planctomycetes* and *Verrucomicrobia*. The evolutionary significance of this, if there is any, is not clear.

In some genera we observed a wide range in the number of TFRs in different species. For example, among the *Mycobacterium* spp., the pathogenic *M. tuberculosis* encodes 49 TFRs, *M. leprae*, known which is to have a reduced genome, encodes only 10, and the environmental isolates *M. abscessus* and *M. smegmatis* encode 138 and 137 TFRs, respectively. These data indicate a general trend that the number of TFRs encoded by an organism may reflect the diversity of environmental conditions that the organism encounters. Bacteria that grow in changeable niches, in particular the soil, are often enriched for TFRs while those that grow in close association with a host organism are not.

Conservation of TFRs

The availability of genome sequences allows us to examine the conservation of TFRs between strains and species. These comparisons may help to reveal TFRs associated with virulence traits or to distinguish newly acquired TFRs involved in specific adaptive responses from conserved TFRs more likely to be involved in regulating basic physiological processes. For example, a comparison of the TFRs in *E. coli* K-12 MG1655 and *E. coli* O157 EDL933 reveals that the two strains share 12 TFRs and that *E. coli* K-12 MG1655 encodes a single additional TFR not present in *E. coli* O157 EDL933. In *E. coli* O157 EDL933, one TFR, BdcR (formerly YjgJ), is truncated and lacks the DNA-binding domain. Further analysis indicates that this truncation is conserved in other O157 genomes as well as the genomes of some *Shigella* species. BdcR is a regulator of BdcA, a novel c-di-GMP-binding protein involved in biofilm dispersal (28). BdcR expression is thought to be regulated by NsrR, a protein that is involved in sensing nitric oxide (29) and that is also known to regulate other genes required for motility and biofilm development. While data on BdcR function are scant, the conserved deletion in *E. coli* O157 indicates that it may play a role in regulating an aspect of virulence.

A comparison of the TFRs in *Pseudomonas aeruginosa* PAO1 and the multidrug-resistant taxonomic outlier PA7 reveals that they have 36 TFRs in common and reveals TFRs unique to each strain that may play a role in the differences in virulence observed between strains. PAO1 encodes five TFRs absent in PA7 (PA1241, PA1290, PA2020, PA2766, and PA2931), while PA7 encodes two TFRs absent from PAO1 (PSPA7_2630 and PSPA7_4004). The PA7-specific TFRs are encoded within genomic islands of this isolate (30). PA2020, MexZ (also see TFRs and Antibiotic Resistance below), encodes a known regulator of the MexXY antibiotic resistance efflux pump (31). Mutations in MexZ are associated with isolates from chronic infections and small-colony variants (32, 33). In PA7, MexZ is truncated, lacking the DNA binding-domain, which leads to overexpression of MexXY and increased aminoglycoside resistance in this isolate (34).

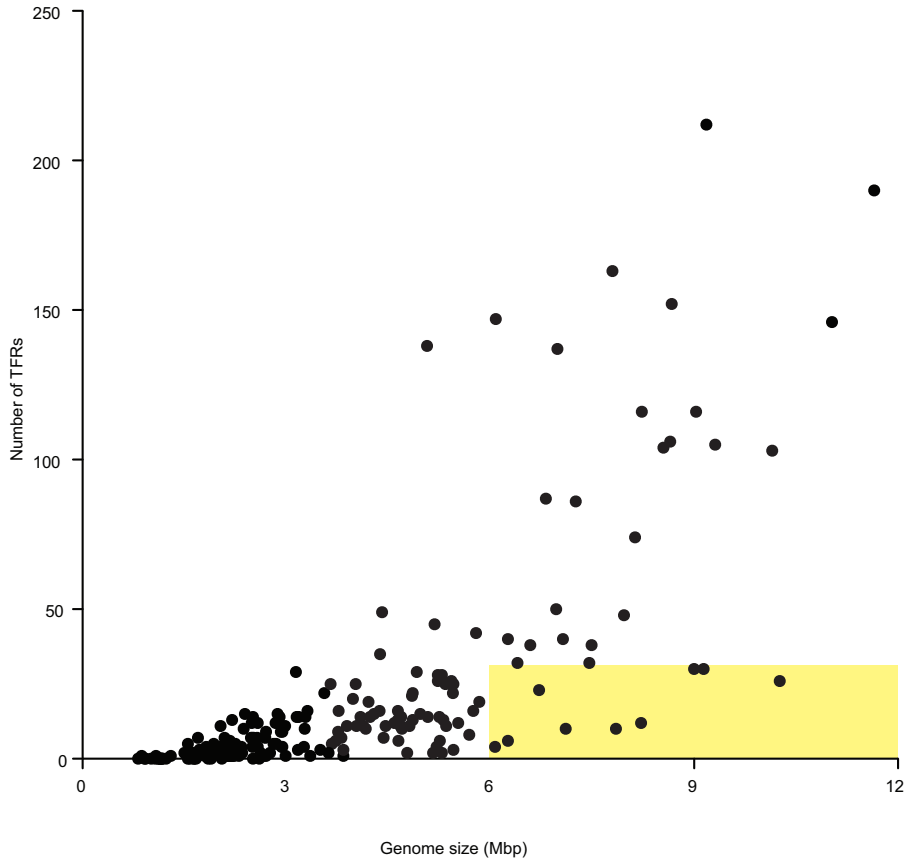

FIG 3 Distribution of TFRs in sequenced genomes. Large genomes with a low number of TFRs are highlighted with a yellow box.

Analyses of TFR conservation can be expanded to include many different species of the same genus. Conservation at the genus level may help to distinguish TFRs more likely to be involved in regulating basic cellular processes (e.g., fatty acid metabolism) as opposed to adaptive functions (e.g., resistance to specific antibiotics) and may point to more recently acquired traits. Our analysis of TFRs from members of the genus *Streptomyces*, the majority of which encode over 100 TFRs, reveals five TFRs that are conserved in all of the close to 70 strains sequenced as of 26 April 2013, with another seven TFRs highly conserved and missing in only one strain. One of these TFRs is more broadly conserved in *Actinobacteria*, while another two have been implicated in the regulation of antibiotic production in members of the genus (6, 35). We surmise that all 10 of these TFRs play an important role in regulating general processes important to antibiotic production and development in *Streptomyces*, while less conserved TFRs are more likely to play a role in regulating specific adaptive functions such as the catabolism of a specific carbon source or resistance to a specific antibiotic. It is interesting to note that four of the five conserved TFRs are type III TFRs (see "Predicting Target Genes" below) and that the regulatory targets cannot be predicted based on genomic orientation.

Predicting Operator Sites

Many TFRs bind palindromic, and often repeated, DNA operator sequences. Informatics approaches to identifying TFR operator sequences have been applied to small numbers of TFRs with success (24). In our experience, however, operator sites for TFRs of unknown function are often difficult to reliably predict. In many cases there is no obvious palindrome, and in others there are palindromes upstream of genes encoding TFRs or predicted targets that do not interact with the cognate TFR. In some cases, these may represent binding sites for other transcription factors. Ramos et al. (14) made use of protein-DNA crystals for QacR and TetR to identify amino acid positions that may generally be important in protein-DNA interactions and give specificity for a particular TFR for its operator sequence. It would be interesting to evaluate this approach to validate potential operator sequences identified through palindrome analysis or to perhaps predict the operator DNA sequence that is recognized by a TFR. Additional information such as DNase I footprinting can aid in the prediction of TFR operator sites from DNA sequence information (23).

Predicting Target Genes

TFRs can be classified into three types based on the orientation and proximity of their structural gene relative to adjacent genes on the chromosome (Fig. 4), and these relationships can be used to predict the regulatory target gene(s) of the TFR (23). The majority of TFRs are classified as type I: their genes show a divergent orientation to one of the adjacent genes, as is the case for *tetR* and *tetA*. This relationship is very predictive of a regulatory relationship in those cases where the intergenic region between the two genes is less than ~200 bp. A longer intergenic region does not rule out a possible regulatory relationship; however, it is more rare

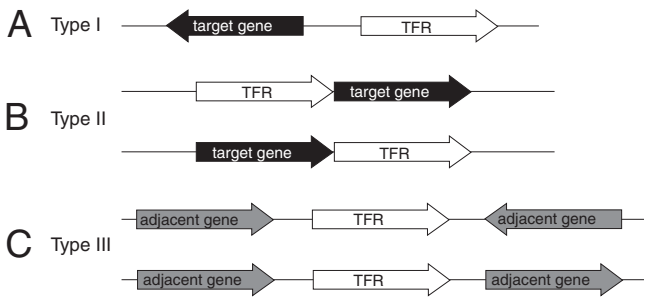

FIG 4 Classification of TFRs based on the orientation and proximity of adjacent genes. (A) Type I TFRs are transcribed divergently from an adjacent gene. A regulatory relationship is predicted when this intergenic region is less than 200 bp. (B) Type II TFRs are predicted to be cotranscribed with and to regulate an adjacent gene based on a distance of less than 35 bp between genes. (C) Type III TFRs show neither of the above-described relationships with adjacent genes, and a regulatory relationship with the adjacent genes cannot be predicted.

in these cases. Type II TFRs are predicted to be cotranscribed with one or more adjacent genes based on orientation and a short distance (less than 35 bp) between genes. The majority of characterized TFRs are known or believed to be autoregulatory, and therefore type II TFRs would also be predicted to regulate the expression of cotranscribed genes. It should be noted, however, that an extensive investigation into autoregulation by TFRs is lacking, and certainly exceptions have been identified (e.g., AmtR [36–38]). In some cases, autoregulation is assumed based on other data (e.g., DNase I foot printing analysis for ActR [23]) but direct evidence is not available. The genes encoding type III TFRs show neither of these relationships with their neighboring genes. In these cases, putative regulatory relationships with neighbors, while they may exist, cannot be predicted by genomic orientation.

Using this classification for TFRs, we can begin to take an inventory of the types of gene products regulated by TFRs (23). This inventory reveals that while the best-characterized TFRs do indeed regulate the expression of efflux pumps like the founding member of the family TetR, a large majority of TFRs actually regulate genes encoding cytoplasmic proteins. These proteins are almost exclusively predicted to be enzymes, and the diversity is extraordinary and includes all of the known functional classes (23). The biochemical functions of most of these enzymes are unknown.

Predicting Ligands

At this time, inducing ligands are known for 61 TFRs but remain unidentified for the vast majority of TFRs, including many of those that have been at least partly characterized. We have employed phylogenomics as a tool to predict ligands for TFRs of unknown function (25). Using this approach, we successfully identified the antibiotic kijanimicin as the inducing ligand for a previously uncharacterized TFR, KijR from *Streptomyces coelicolor*. Identifying the inducing ligand for KijR provided crucial insight into the function of its target gene, *kijX*, which acts as a kijanimicin deglycosylase. As discussed above, the majority of TFRs regulate enzymes of unknown function, and methods to identify the small-molecule ligands for TFRs will prove invaluable in determining the substrates and enzymatic functions carried out by the enzymes they regulate.

TFRs encoded in antibiotic biosynthesis clusters are known to interact with the products of those clusters (see TFRs and Antibiotic Resistance below) and can help us make predictions for ligands bound by TFRs of unknown function. For example, TFRs in the biosynthesis clusters for two structurally related polyether ionophores, calcimycin and monensin (TFRs SchR3 and MonRII, respectively), form a group in our phylogenetic analysis with the TFR of unknown function SSQG_00958 (Fig. 5A). Based on this clustering, we predict that SSQG_00958 binds a similar polyether ionophore and is involved in regulating resistance to the same molecule. SSQG_00958 is transcribed divergently from a putative exporter encoded by SSQG_00957. In another example, the gene encoding MlaM is located in the biosynthesis cluster for a macrolactam antibiotic and in our phylogenetic analysis falls into a larger group with two other TFRs, BecM and Strop_2766, located in the biosynthesis clusters for structurally related molecules (Fig. 5B). This cluster also contains numerous other TFRs of unknown function which we predict bind similar macrolactam antibiotics.

Ligand predictions based on phylogenomics are not limited to antibiotics. For example, BreR binds bile acids and is thought to be important to the survival of *Vibrio cholerae* in the intestinal tract (39). BreR and AefR share 30% identity (67% similarity) and grouped together in our analysis (Fig. 5C). AefR is involved in regulating quorum sensing and epiphytic fitness in the plant pathogen *Pseudomonas syringae*, but its inducing ligand is unknown (40). Given the similarities between BreR and AefR, we predict that the AefR-inducing ligand may be a phytosterol. Phytosterols share structural similarities with bile acids, and some (e.g., tomatidine) are known to have antimicrobial activity (41).

Combining information on TFRs from both phylogenomics and genomic context can also provide a powerful tool for predicting small-molecule ligands for TFRs. As the majority of TFRs are transcribed divergently from their target genes, in cases where the function of the target gene is known, this organization can lead to a prediction of a possible TFR ligand. For example SCO4099 from *S. coelicolor* is transcribed divergently from SCO4098, which encodes a putative streptogramin A acetyltransferase (*vat*) homolog. Our phylogenomics analyses coupled with additional database searches identify numerous TFRs sharing high similarity to SCO4099 in other actinomycetes; however, no ligands have been identified for any of them (Fig. 6) (25). These homologs are transcribed divergently from additional gene products implicated in resistance to streptogramin antibiotics (e.g., *vgaA* and *vgbA*) as well as gene products known to be involved in antibiotic resistance but not specifically in streptogramin resistance (e.g., *mgtA/oleD* and *ereA*). Using a combination of genomics approaches, we can predict that SCO4099 and related TFRs may bind a streptogramin antibiotic and that the genes regulated by these TFRs include both known and potentially novel streptogramin resistance genes.

TFR STRUCTURAL BIOLOGY

General Structure of TFRs

X-ray crystal structures are currently available for close to 200 TFRs. Despite the vast sequence divergence seen in TFRs, structural data reveal that all family members share common structural features both in the DNA-binding domains (which are conserved in terms of primary sequence) and also in the ligand-binding domains (which are not) (24) (Fig. 7). The overall conserved structure of TFRs consists of nine α helices. The DNA-binding domain is composed of helices 1 to 3. Helices 2 and 3 form a helix-turn-

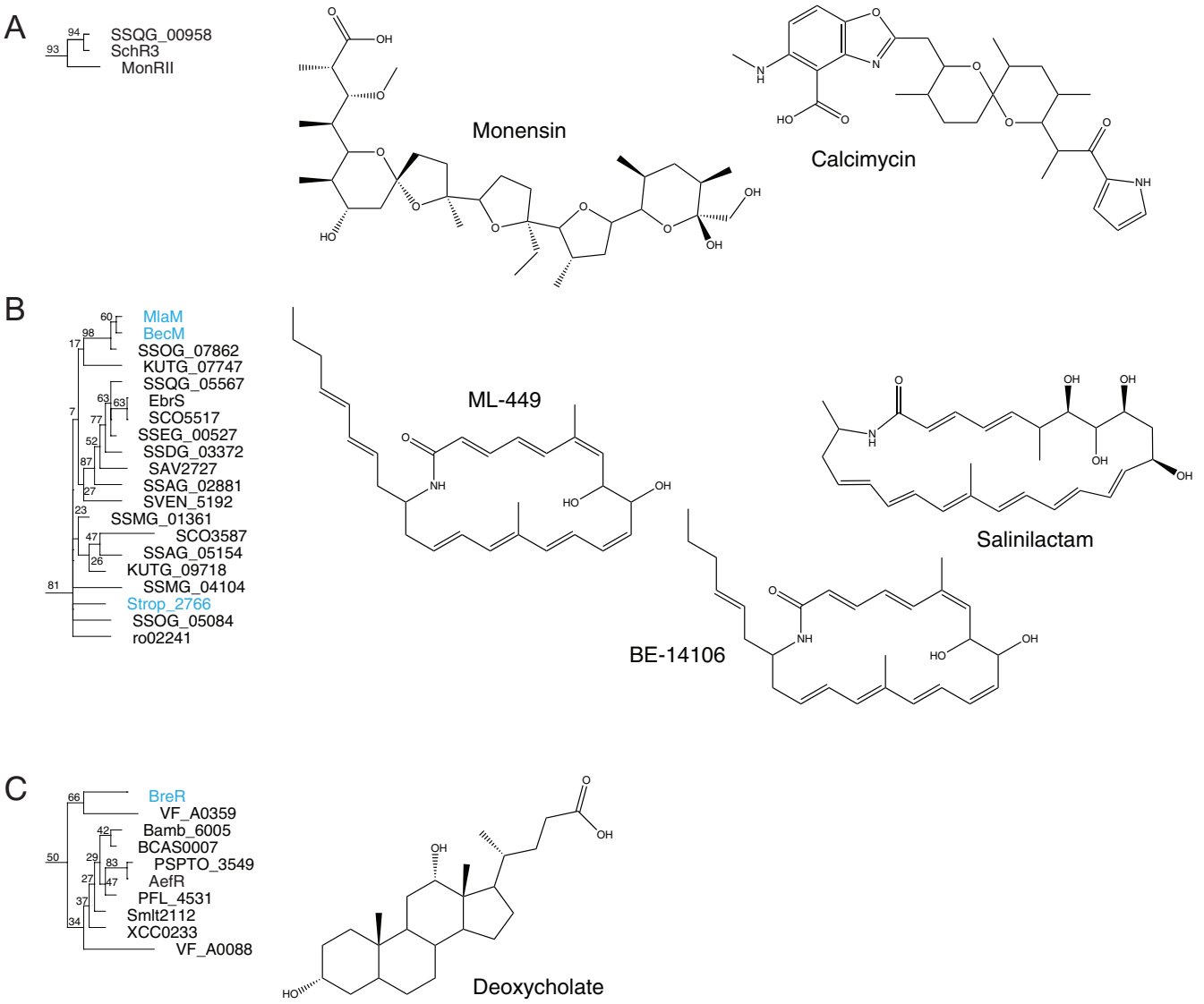

FIG 5 Phylogenomics can be used to predict small-molecule ligands for TFRs of unknown function. (A) The TFR of unknown function SSQG_00958 is predicted to bind a polyether ionophore based on grouping with MonRII and SchR3. (B) TFRs encoded in the biosynthesis clusters for macrolactam antibiotics cluster together, leading to the prediction that all of the TFRs in this group interact with macrolactam antibiotics. (C) AefR may recognize a phytosterol based on clustering with BreR. (Adapted from reference 25.)

helix motif, with helix 3 serving as the recognition helix that fits into the major groove upon DNA binding. The length of helix 1 is variable and can range from 12 to 23 residues (24). In many TFRs, helix 1 is preceded by a positively charged region responsible for making contacts with the DNA minor groove (see below) (42).

The ligand-binding domain is formed by conserved helices 4 to 9. Contacts between helix 1 of the DNA-binding domain and helices 4 and 6 of the ligand-binding domain link the two domains and are responsible for transmitting structural changes between the two domains upon ligand binding (see below). The ligand-binding domain can be divided into two structural subdomains. Helices 5 to 7 form a central triangle, while helices 8 and 9 make up the dimerization interface, forming a four-helix bundle with the same helices from the other monomer. In addition to the nine conserved helices, some TFRs, including TetR itself, contain a long insertion between helices 8 and 9 that may be involved in additional contacts to make up the dimer interface. It has been noted that while TetR serves as an important model for the family, its structure, along with that of another model TFR, QacR, is actually atypical compared to the majority of TFRs of known structure (24).

Interactions of TFRs with DNA

As of February 2013, structures have been solved for seven TFR-DNA complexes: CgmR, DesT, HrtR, QacR, SimR, TetR, and TM1030 (42–47). Based on the TFR-DNA structures currently available, it is clear that while TFRs share structurally similar DNA-binding domains, the mechanisms involved in DNA binding differ in significant ways between proteins. As discussed above, the DNA-binding domain is composed of helices 1 to 3, with helix 3 being responsible for the majority of DNA contacts. Helices 3 and 3′ recognize adjacent major grooves; thus, the spacing be-

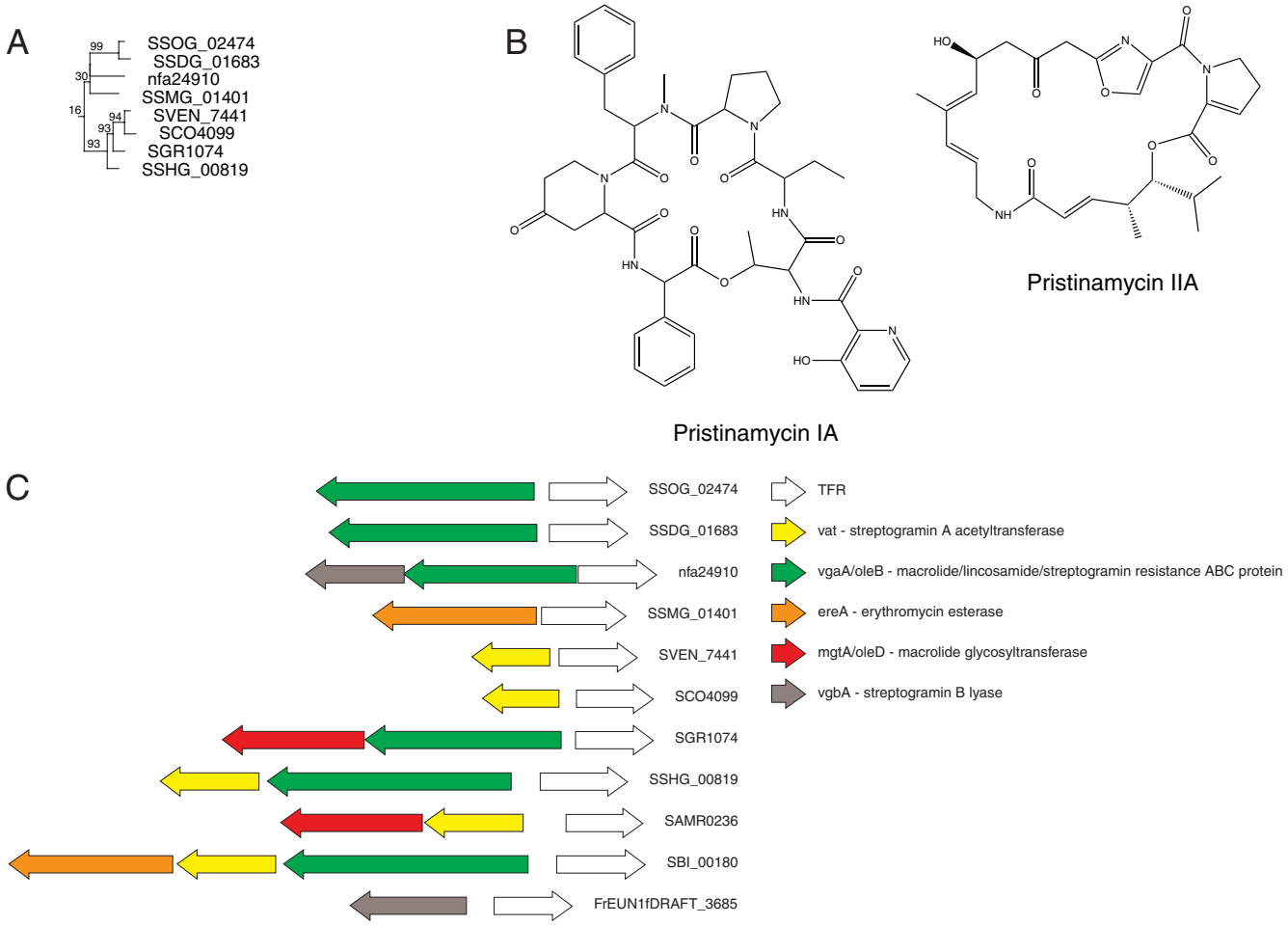

FIG 6 Combining information from genomic context with phylogenomics can also lead to ligand predictions for TFRs. (A and C) All of the TFRs in the group shown (A) (data are from reference 25) are type I TFRs predicted to regulate genes involved in streptogramin resistance (C). (B) Structure of the streptogramin antibiotic pristinamycin.

tween these two helices in the TFR dimer is crucial for structural compatibility with stable DNA binding. In all cases investigated to date, this spacing is the target of conformational changes associated with ligand binding (see below). In general, TFR binding seems to induce a bend in the DNA, although at present there is no sequence or structural explanation for what determines either the direction of bending (toward or away from the TFR) or the degree of bending (43, 44, 47).

For some TFRs (e.g., TetR and QacR) the majority of TFR-DNA contacts are base specific, while for others (e.g., CgmR, DesT, HrtR, and SimR) the majority of TFR-DNA contacts are with the phosphate backbone. In the TetR-DNA complex, Lys48, located C-terminal to the DNA-binding domain, also makes an important DNA contact. The equivalent residue in SimR, Lys71, makes a similar contact, but this contact is absent from other TFR-DNA structures, including DesT and QacR. In SimR, additional DNA contacts are made between the N-terminal "arm" of SimR and the DNA minor groove. Positively charged arginine residues in the arm of SimR mediate these contacts. Sequence alignments and structural predictions reveal that a similar arm may be found in the majority of TFRs (42).

The QacR-DNA complex is distinct from that of other TFRs in that two QacR dimers bind cooperatively. Unlike many other transcription factors (e.g., the lambda phage repressor cI), where this cooperativity is due to protein-protein interactions between adjacent dimers (48), in QacR, cooperative binding is brought about by an alteration in the structure of DNA. Specifically, the interaction of QacR with DNA causes local underwinding that increases the distance between adjacent major grooves, and it is this conformation that most favorably forms the repressed complex with two QacR dimers. A slight widening of the major groove was also seen in the structure of DesT in complex with oleoyl coenzyme A (oleoyl-CoA) and DNA, indicating that this structural change is not limited to the QacR-DNA complex.

TFR-Ligand Interactions

At this time, ligands have been identified for 61 TFRs and X-ray crystal structures solved for 21 TFR-ligand complexes (Table 2). This information allows us to begin comparing the types of ligands recognized by TFRs and the mechanisms of ligand recognition. The known TFR ligands are extraordinarily diverse and include antibiotics, bile acids and other toxic molecules, cell-cell signaling molecules, carbon sources, proteins, fatty acids and fatty acid derivatives, and metal ions (Fig. 1, 5, and 6). This diversity

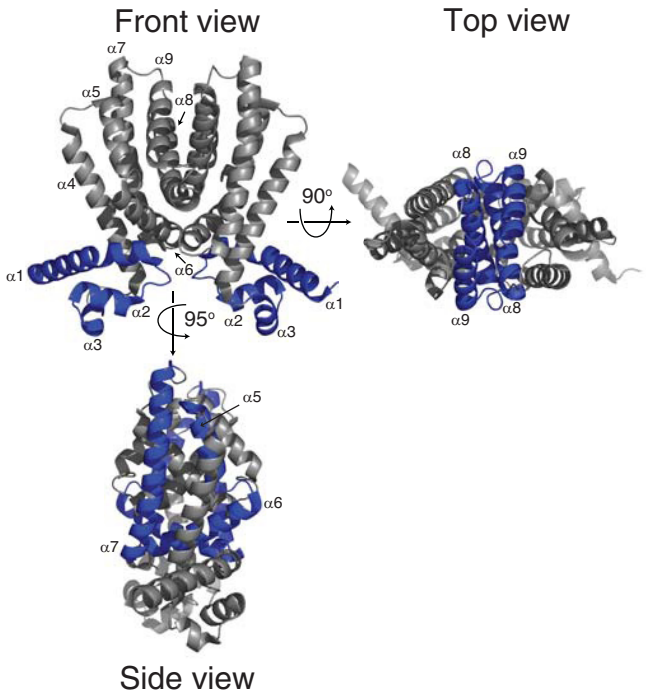

FIG 7 TFRs share nine conserved α helices. In the front view, the DNA-binding domain is made up of helices 1 to 3. In the side view, helices 5 to 7 in the ligand-binding domain form a central triangle. In the top view, helices 8 and 9 from each monomer form a four-helical bundle that makes up the dimer interface. The structure of Rha06780 (PDB ID 2NX4) is shown, as it shows a structure typical of TFRs (24).

supports a role for TFRs in regulating an equally diverse array of cellular processes from basic carbon and nitrogen metabolism to quorum sensing and antibiotic resistance. Structures are available for TFRs in complex with simple ligands such as citrate and resorcinol (49) to very complex molecules such as acyl-CoA derivatives (44) and antibiotics with multiple functional groups such as simocyclinone (50).

There are many ways that TFRs can interact with ligands. Structural data suggest that there are at least three different points at which ligands can enter a TFR ligand-binding site (Fig. 8). For example, ActR, QacR, SmeT, TetR, and TtgR all have a "side entry" opening distal to the dimerization interface that is believed to be the site of access for different ligands (22, 51–54). Ligands appear to enter CmeR, CgmR, HrtR, LfrR, and SimR via an entry point closer to the "front" of the protein (43, 46, 50, 55, 56). Finally, DesT, EthR, and FadR exhibit a relative "top entry" (44, 57, 58). It is unclear what, if anything, these differing mechanisms of ligand entry mean in terms of the type of ligand bound or the structural influence of ligand binding. For RolR and RutR, which bind resorcinol and uracil, respectively, there is no obvious entrance to the ligand-binding pocket (49). Rather, the ligand is trapped inside an otherwise inaccessible proteinaceous cage (Fig. 8).

Each tetracycline-binding pocket in TetR is composed primarily, but not exclusively, of residues from an individual monomer (22). This is also seen for the ligand-binding pockets of the majority of TFRs (e.g., ActR, CmeR, and QacR [53, 54, 56]). In contrast, the SimR ligand-binding cavity is composed of residues from both monomers such that each binds either the aminocoumarin or the angucyclinone moiety of the simocyclinone ligand (50).

Two molecules of Mg^{2+}-tetracycline are bound by each dimer of TetR (22). This is also the case for many TFRs (e.g., SimR, CmeR, and MphR [50, 56, 59]), but different drug-binding stoichiometries are seen in some others. In the case of ActR, each ActR dimer is capable of binding either two molecules of actinorhodin or four molecules of (*S*)-2,4-dinitrophenyl acetate [(*S*)-DNPA] (54). In contrast, each dimer of LfrR binds only a single molecule of proflavine (55). Like LfrR, the majority of QacR-ligand structures show a single ligand within one monomer of each dimer. However, one structure of QacR in complex with two different ligands, ethidium and proflavine, within the same monomer has been solved (60). For CgmR, different binding stoichiometries are seen for different drugs, and the size of the drug is thought to play a role in the number of molecules required for CgmR derepression (43). TtgR also shows an interesting stoichiometry of binding to the plant antimicrobial phloretin, binding two molecules within one monomer and one in the other (51), while in SmeT, two molecules of triclosan were seen within a single monomer, while none were observed in the other (61).

Structures are available for four TFRs (CgmR, EbrR, QacR, and TtgR) in complex with different drugs, and analysis of these structures may shed light on how a single TFR may recognize a diverse set of ligands (43, 51, 53, 60). Based on the structures currently available, different drugs appear to be accommodated by different drug-binding sites within a single binding cavity. The structure of QacR has been solved in complex with six different cationic drugs. It shows a large binding pocket (1,100 $Å^3$) lined with negatively charged residues that form several separate drug-binding sites. In CgmR, ethidium bromide and methylene blue were found in the same inducer-binding pocket but were bound by different networks of hydrogen bonds. Structures are available for TtgR in complex with five different ligands, two antibiotics and three plant antimicrobials. TtgR contains a large, mainly hydrophobic, binding pocket with two distinct drug-binding sites: a high-affinity site and a general binding site. The high-affinity site is smaller and was occupied by only one of the five TtgR ligands. The general binding site is broader and was found to be occupied by all five ligands.

The first two reported structures of EthR were solved in conjunction with a fortuitous ligand, in once case hexadecyl octanoate (58) and in the other two cases uncharacterized molecules consisting of a six-membered ring (62). These structures have been critical in the design of synthetic EthR ligands (see below), and subsequent structures of EthR have been solved in complex with a number of these molecules (63–65). In one study, two related analogs were found to bind EthR with different orientations, supporting the extremely plastic nature of the EthR ligand-binding pocket (63). While EthR is known to recognize a large variety of ligands, only a small number of residues were found to be in contact with all ligands (66).

Similar to the case of EthR, the structure of CmeR shows how two structurally similar molecules can fit very differently into the same binding pocket (56). The structure of CmeR has been solved in complex with two structurally similar bile acids, taurocholate and cholate. Despite the similarity of these molecules, they were found within the same binding pocket but in opposite orientations, lying antiparallel to each other. Not only is DesT able to recognize different ligands, both saturated and unsaturated fatty acids, but its ability to do so is crucial to its function (44). Binding

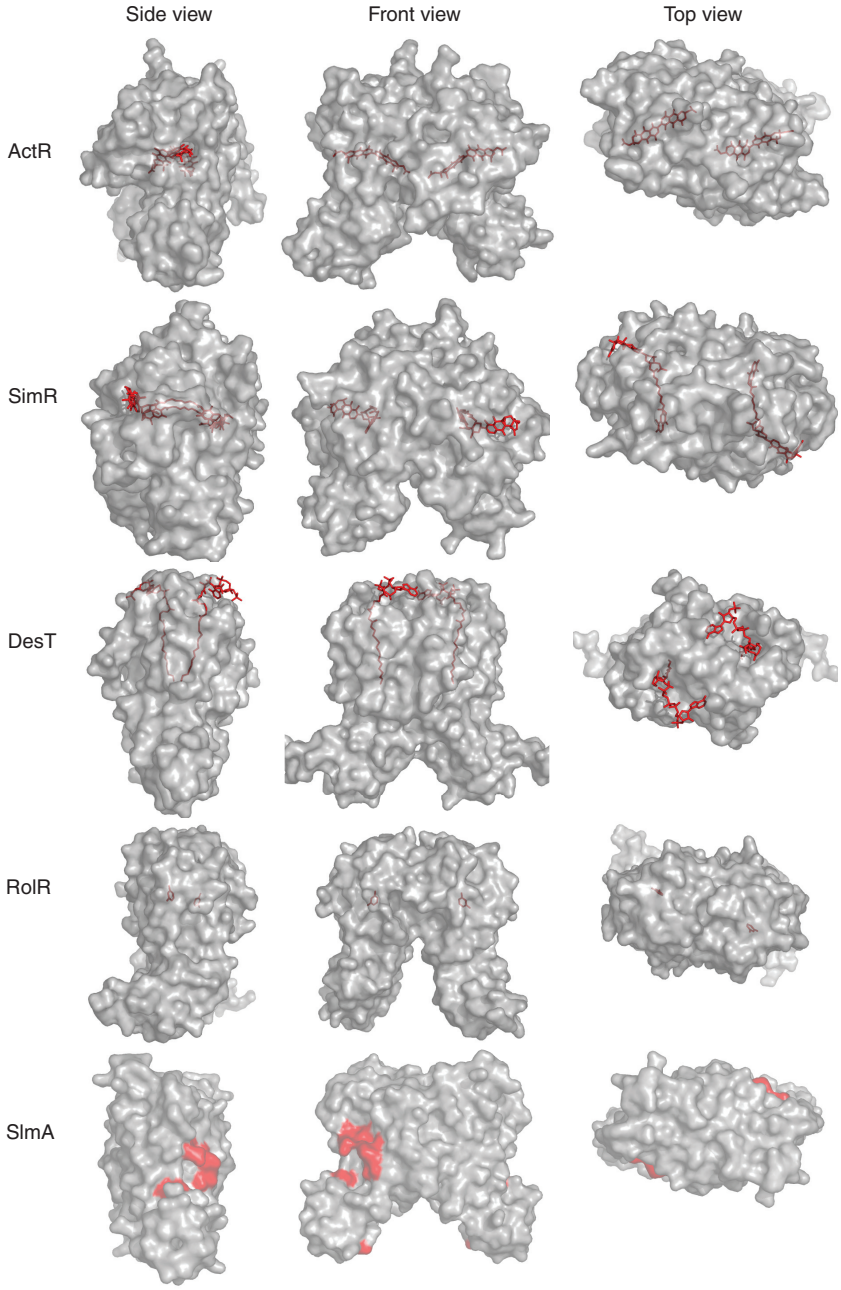

FIG 8 TFRs display different ligand entry points. Based on current TFR-ligand structures, the ligand-binding cavity may be accessible from the side (e.g., ActR), front (e.g., SimR), or top (e.g., DesT) of the TFR. In some structures (e.g., RolR), the ligand is not accessible to the external environment and the entry point cannot be determined. SlmA interacts with a protein rather than a small-molecule ligand. Residues involved in protein-protein interactions are colored in red.

of the unsaturated oleoyl-CoA increases DNA-binding affinity, while the saturated palmitoyl-CoA serves as the inducer. DesT activity is regulated by the ratio of the two different ligands rather than through a single ligand. A Phe-rich cluster in DesT senses which ligand is bound. This changes the hydrophobic core to create a binding cavity tailored to each particular ligand.

Crystal structures are also available for seven uncharacterized TFRs in complex with bound ligands (3EGQ, 3CJD, 3KKD, 2QIB, 2D6Y, 4ICH, and 2IEK). It is difficult to determine if these TFR-ligand interactions are biologically relevant, but in at least one case, the genes adjacent to the TFR on the chromosome, and hence the predicted regulated genes (23) (see Genomics of TFRs above), indicate a potentially relevant relationship. The TFR Jann_2994 from the alphaproteobacterium *Jannaschia* sp. strain CCS1 was crystalized with stearic acid (PDB ID 3CJD). Jann_2994 is adjacent to a putative PspA homolog, which is potentially involved in regulating cytoplasmic membrane integrity as well as a putative fatty acid desaturase.

At least three TFRs, AmtR, DhaS, and SlmA, are known to interact with proteins rather than small-molecule ligands (GlnK, DhaQ, and FtsZ, respectively) (67–69). Residues of SlmA involved in interactions with the cell division protein FtsZ have recently

been identified (70). These residues form an active site on the ligand-binding domain that in the crystal structure of SlmA is partially blocked by the DNA-binding domain (Fig. 8). The authors proposed that in the DNA-bound form of SlmA, the entire FtsZ interaction interface would be exposed, with implications for SlmA function (see TFRs and Cell Division below) (70).

Two TFRs, SczA and ComR, bind metals, but the molecular details of these interactions are not known (71, 72). Further structural studies will provide clues as to the mechanisms surrounding how TFRs specifically recognize metal ions.

Mechanism of Induction by Ligands

Structures are available for six TFRs (TetR, QacR, HrtR, DesT, SimR, and CgmR) in both DNA-bound and ligand-bound conformations, providing insight into the structural mechanism of derepression (22, 42–47, 50, 53). It has been noted that in most apo-protein structures, the TFR most closely resembles the ligand-bound or induced form rather than the DNA-bound form. It is therefore unlikely that the comparison of apo and ligand-bound structures provides a meaningful insight into induction and that it is necessary to compare the ligand-bound and DNA-bound forms.

In all cases, ligand binding is associated with increased separation of the DNA-binding domains of the two TFR monomers relative to the DNA-bound form. This may be accompanied by further conformational changes involving helix 4 and helix 6, which are in direct contact with the DNA-binding domain. In TetR, ligand binding causes a shift in helix 6 resulting in the pendulum-like motion of helix 4. Using equilibrium protein-unfolding experiments, Reichheld et al. (73) provided evidence that TetR does not occupy two distinct folded states (i.e., DNA bound and tetracycline bound) but rather that ligand binding increases the folding cooperativity between the N- and C-terminal domains. It was suggested by Reichheld et al. (73) that this increases the stability of a conformation in which the DNA-binding domains are too far apart to support binding to adjacent major grooves in the DNA.

Similar to the case for TetR, a pendulum-like motion was noted in helix 4 of both QacR and CgmR, but in these cases, ligand binding caused a coil-to-helix transition in helix 5 and a relocation of helix 6 in QacR. In CgmR, a widening of the inducer-binding pocket and shift in helix 6 was observed. In HrtR, heme binding was shown to cause a coil-to-helix transition in helix 4, resulting in a rigid-body motion of the DNA-binding domain to an orientation not compatible with DNA binding. The case of DesT is perhaps not as simple, as DNA-binding and induced forms of the protein are both bound to ligands, albeit different ones. In the DNA-free form (bound to the inducing ligand palmitoyl-CoA as opposed to oleoyl-CoA), a helix-to-coil transition of helix 4 is seen along with an ordering of the L8-L9 loop and movement of helix 6 and helix 7. These changes in DesT again result in a widening of the distance between the DNA-binding domains. SimR represents yet another variation, where there is no reorientation between the DNA-binding and ligand-binding domains but rather a rigid-body motion of the two SimR monomers relative to each other that results in a widening between the two DNA-binding domains.

It is difficult to posit a universal structural model for the transition between the repressing and induced conformations for TFRs, and indeed, it is unclear whether there are true commonalities throughout the family. Certainly key structural elements, including the conserved helices of the DNA-binding domain and the conserved helix 5 to 7 triangle and four-helix dimerization interface, are relevant. While at first glance it may be difficult to directly apply the Reichheld model for allosteric regulation of TetR (73) to SimR given that there is no reorientation between the DNA-binding and ligand-binding domains in the case of SimR, structural flexibility along the monomer interface may be important in this case. The ligand-binding cavity of SimR is composed of residues from both monomers, and as a result ligand binding will undoubtedly decrease the flexibility between them. Recent work has challenged the Reichheld model (74); however, this work was based primarily on X-ray crystallographic analysis of the protein bound to artificial peptide inducers and therefore should be interpreted with caution. Our view is that nuclear magnetic resonance (NMR) analysis of one or more TFRs, preferably for those where there are X-ray data on both the ligand- and DNA-bound forms (e.g., CgmR, DesT, HrtR, QacR, SimR, or TetR), in which the structural transitions that occur upon ligand binding are monitored would be an ideal means of settling debate in this area.

TFRs AND ANTIBIOTIC RESISTANCE

There are numerous TFRs involved in regulating resistance to antibiotics and other toxic compounds. These TFRs can be divided into three categories: (i) TFRs regulating self-resistance in antibiotic-producing organisms, (ii) TFRs regulating specific antibiotic resistance in nonproducing organisms, and (iii) TFRs regulating multidrug resistance.

TFRs Regulating Self-Resistance in Antibiotic-Producing Organisms

Numerous TFRs have been identified in the biosynthesis clusters for antibiotics and other secondary metabolites in species of *Streptomyces* and related actinobacteria. Of these, six TFRs, i.e., ActR, KijA8, LanK, PhlF, SimR, and VarR, have been shown to bind the products of the biosynthetic pathways in which they are encoded (25, 75–79). These TFRs primarily regulate the expression of efflux pumps required for antibiotic export but may also regulate the expression of late-stage biosynthetic genes.

Actinorhodin is a benzoisochromanequinone antibiotic produced by *S. coelicolor*. The biosynthetic pathway for this compound is encoded in a 22-kb region that includes the *actR* gene and its target operon *actAB*, which encodes two efflux pumps believed to export actinorhodin from the cell. The biosynthesis of actinorhodin involves a typical type II polyketide synthase that first generates an 18-carbon octaketide (80). This molecule is tailored into a 3-ring intermediate, and, late in the pathway, two of these intermediates are covalently joined to generate the mature six-ring compound. ActR binds both the final biosynthetic product actinorhodin and three-ring biosynthetic intermediates, including (*S*)-DNPA (79). Genetic evidence suggests that in actinorhodin-producing cells (*S*)-DNPA and/or other 3-ring intermediates serve to activate the expression of efflux genes, the only known self-resistance mechanism, before the final product is synthesized (81). Furthermore, there are now several reports that the export proteins are required for efficient, high-yield biosynthesis of actinorhodin (81, 82). The biochemical basis for reduced actinorhodin biosynthesis in cells defective in the *actAB* operon is not well understood, but it has been interpreted as evidence that initial activation of the actinorhodin export genes is primarily dependent on intermediates. However, it is also clear that sustained

expression of the actinorhodin efflux pumps throughout the culture (i.e., including cells that produce actinorhodin and those that do not) requires the actinorhodin final product (81). Thus, actinorhodin is believed to act as a cell-cell signal to trigger export and resistance in nonproducing cells.

Like ActR, LanK and SimR are also able to bind both the final products of the biosynthetic pathways in which they are encoded and biosynthetic intermediates. LanK from *Streptomyces cyanogenus* S136 is located in the biosynthesis cluster for the glycosylated angucyclic polyketide antibiotic landomycin A. LanK regulates both the landomycin A efflux pump encoded by *lanJ* and the downstream gene *lanZ1* (78). LanZ1 is an epimerase required for synthesis of sugar residues required for later-stage landomycin biosynthesis. Thus, as is the case for ActR, at least one step in the induction of the LanK target operon involves the interaction of the repressor with an immature landomycin intermediate. TFRs are also located in the biosynthesis clusters for the related angucyclinone antibiotics urdamycin and saquayamycin, but the role of these TFRs in regulating antibiotic biosynthesis and export has not been investigated (83, 84).

SimR is located in the biosynthesis cluster for simocyclinone D8 in *Streptomyces antibioticus* Tü 6040 (85, 86). Simocyclinone D8 is a structurally complex inhibitor of DNA gyrase (87, 88). The final molecule is composed of four parts: an angucyclic polyketide, a D-olivose sugar, a tetraene linker, and an aminocoumarin moiety. SimR regulates expression of the simocyclinone efflux pump encoded by *simX* and is induced by both simocyclinone D8 and the intermediate simocyclinone C4, which lacks the aminocoumarin functional group (76). It is not clear, however, that the interaction of SimR with the C4 intermediate is biologically relevant. Unlike the ActR case, where intermediates are bound more tightly than the finished product, or the LanK case, where induction is required for the completion of biosynthesis, the C4 intermediate binds more weakly than the mature D8 molecule, and there are no known biosynthetic steps that depend on the SimX export protein.

TFRs are encoded in many of the antibiotic biosynthesis gene clusters found in actinomycetes; however, they are also associated with the biosynthesis of other classes of compounds in a great many organisms. For example, PhlF is located in the 2,4-diacetylphloroglucinol biosynthesis cluster of *Pseudomonas fluorescens* (89). Biosynthesis of 2,4-diacetylphloroglucinol is of interest, as it occurs via a type III polyketide synthase (PKS) thought to be rare in bacteria (90). PhlF binds to the intergenic region between *phlF* and *phlA*, repressing expression of the *phlABCD* operon (75). DNA binding is enhanced in the presence of salicylate and disrupted by the biosynthetic product of the cluster 2,4-diacetylphloroglucinol.

TFRs are also present in the biosynthesis clusters for diverse polyketides, including ansamycins (e.g., *rifQ* in the rifamycin cluster [91]), macrolactams (e.g., *mlaM* in the ML-449 cluster [92]), and polyether ionophores (e.g., *schR3* in the calcimycin cluster [93]). TFRs are not limited to polyketide biosynthesis clusters but are found in biosynthesis clusters for nonribosomal peptides (e.g., *acmP* and *acmU* in the actinomycin cluster [94]) and nucleoside antibiotics (e.g., *amiP* in the amicetin cluster [95]).

KijR and Pip from *S. coelicolor* are involved in regulating antibiotic resistance in a nonproducing organism (see below) and are closely related to KijA8 and VarR, respectively (25) (Fig. 9), raising the possibility that KijR and Pip were acquired by horizontal gene

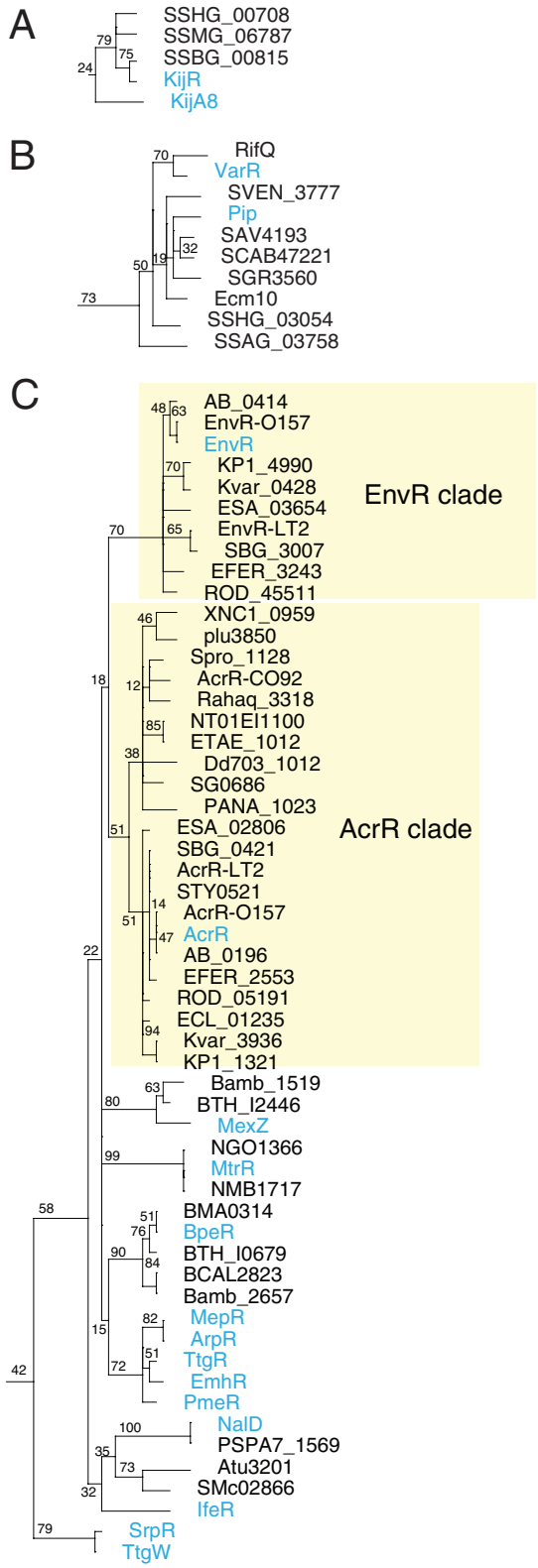

FIG 9 Grouping of TFRs involved in antibiotic resistance. (A and B) KijA8 and KijR (A) and VarR and Pip (B) group together in phylogenomics analysis, indicating that KijR and Pip may have been horizontally acquired from an antibiotic-producing organism. (C) Many TFRs controlling the expression of multidrug efflux pumps cluster together in phylogenomics analysis. (Adapted from reference 25.)

transfer from a producing organism. KijA8 regulates expression of the putative kijanimicin efflux pump encoded by *kijA5* in response to kijanimicin in the producing organism *Actinomadura kijaniata* (25). Similarly, VarR regulates expression of the virginiamycin efflux pump in *Streptomyces virginiae* in response to virginiamycin S (77). Environmental microbes are highly resistant to antibiotics (96) and provide a reservoir for resistance elements in other environmental microbes as well as in clinically relevant pathogens (97, 98). This raises questions as to the possible origins of other TFRs, for example, TetR and MphR of *E. coli*, in producing organisms. No TFR has been identified in the biosynthesis clusters for oxytetracycline or chlorotetracycline, but a TFR is present in the cluster for the glycosylated anticancer tetracycline SF2575, although our analysis does not show a close relationship to TetR from *E. coli* (25, 99). The closest homolog of MphR is, however, found in the environmental microbe *Myxococcus xanthus* (25, 59), revealing possible origins for MphR in the environment.

TFRs Regulating Specific Antibiotic Resistance in Nonproducing Organisms

The first characterized TFR, TetR, the founding member of the family, is the regulator of tetracycline resistance. Despite this, only a limited number of TFRs have been implicated in specific antibiotic resistance in nonproducing organisms: TetR, KijR, MphR, and Pip and the paralogous TFRs LmrA and QdoR.

Like for TetR, the target of Pip in *S. coelicolor* (SCO4025) is efflux pump gene of the major facilitator superfamily, *pep* (SCO4024) (100). Unlike *tetR* and *tetA*, *pip* and *pep* are cotranscribed. As discussed above, Pip shares a high degree of similarity with VarR in the viginiamycin biosynthesis cluster.

KijR and MphR regulate enzymes involved in antibiotic inactivation (25, 101). KijR regulates the expression of *kijX*, which encodes a novel antibiotic deglycosylase, and shares similarity with *kijA8* in the kijanimicin biosynthesis cluster (see below) (25). MphR regulates expression of *mphA*, encoding a macrolide phosphotransferase, and *mrx*, encoding a membrane protein required for high-level resistance (101, 102). Another, unnamed TFR is found upstream of genes encoding a macrolide phosphotransferase (*mphB*) and a putative methyl esterase (*rdmC*-like) required for high-level macrolide resistance in some strains of *E. coli* as well as *Streptococcus uberis* (103). Despite the fact that they both regulate macrolide resistance genes, this unnamed TFR and MphR were found in separate groups in our analysis (25).

LmrA and QdoR are paralogous TFRs in *Bacillus subtilis* that bind plant flavonoids (104). LmrA and QdoR regulate expression of their own genes as well as those for LmrB, QdoI, and YxaH. The LmrA/QdoR regulon is organized into two operons: *lmrA-lmrB* and *qdoR-qdoI-yxaH*. LmrB is an efflux pump of the major facilitator superfamily. QdoI is a quercetin dioxygenase, responsible for flavonoid inactivation. YxaH is a membrane protein of unknown function.

Rather than regulating a specific antibiotic resistance mechanism, EthR from *M. tuberculosis* regulates the expression of EthA, an enzyme required for activation of the antibiotic ethionamide (105–108). While EthA is active against a broad range of substrates, including two other tuberculosis prodrugs, isoxyl and thiacetazone (106, 109, 110), the natural substrate for EthA is an unknown molecule believed to be distinct from ethionamide which is not an inducer of *ethA* expression. Due to its toxicity, ethionamide is currently used as a second-line drug primarily in the treatment of drug-resistant strains of tuberculosis. Activators of EthR are of interest for use in conjunction with ethionamide, as they would increase EthA expression, and therefore activation of ethionamide, allowing for lower ethionamide concentrations to be used (64).

TFRs Involved in Regulating Multidrug Resistance

TFRs are also involved in regulating a number of multidrug resistance pumps, including AcrAB in *E. coli*, which is regulated by AcrR, and MexXY from *Pseudomonas aeruginosa*, which is regulated by MexZ (111, 112). The AcrAB efflux pump in *E. coli* is under the control of several global regulators, including MarA, Rob, SoxS, and SdiA (113, 114). AcrR is thought to play a role in fine-tuning the expression of *acrAB* rather than serving as an on-off switch (112). Nevertheless, mutations in *acrR* alone result in increased expression of *acrAB* and are associated with antibiotic-resistant clinical isolates (115). AcrR has been shown to interact with various synthetic compounds, including ethidium, proflavine, and rhodamine 6G (116); however, the physiological relevance of these ligands for AcrR and other TFRs regulating multidrug resistance pumps such as QacR may be questionable. Clinically, the so-called multidrug resistance pumps, particularly those of the RND family, are a major source of antibiotic resistance in Gram-negative bacteria (117). However, multidrug resistance is typically the result of mutations in the regulators (118) of these pumps, indicating that multidrug resistance is not the native function of these pumps and that they serve other natural functions (119). Identifying *bona fide* interacting partners for the regulators of these pumps, whether they are small-molecule or protein ligands, will help to elucidate their roles under physiological conditions. A role for AcrAB in removing toxic metabolites has been suggested (120), and it would be interesting to test these putative *acrAB* inducers as ligands for AcrR.

The MexXY transporter of *P. aeruginosa* is expressed under conditions of ribosome stress, including the presence of antibiotics that target the ribosome (121). Expression of *mexXY* is controlled by the TFR MexZ and requires ArmZ (PA5471) (122), which interacts with MexZ (31, 123). *armZ* encodes a homolog of RtcB, an RNA ligase involved in recovery from stress-induced RNA damage (124), and is cotranscribed with PA5470, which encodes a homolog of PrfH. PfrH is thought to function as a peptide release factor that recognizes mRNA signals other than normal stop codons, possibly signals that result from RNA damage (125). While antibiotics that target the ribosome induce MexZ expression, MexZ does not appear to interact directly with these antibiotics but rather responds to effects downstream of ribosome disruption. Similarly, while the MexXY efflux pump functions as a multidrug efflux pump, its native function is not antibiotic efflux *per se* but rather its increased expression is a response to ribosome stress. Our phylogenetic analysis reveals a group containing many TFRs regulating putative multidrug efflux pumps (Fig. 9). This group includes, for example, AcrR and EnvR of *E. coli*, MexZ and NalD of *P. aeruginosa*, and MtrR of *Neisseria gonorrhoeae*. Further studies will be required to determine whether this shared grouping is indicative of a common interacting partner (small molecule or protein) for these TFRs and a common function for the efflux pumps that they regulate.

TFRs AND CELL-CELL SIGNALING

GBL Signaling

Gamma-butyrolactone (GBL) signaling molecules are involved in the regulation of antibiotic production and morphological development in *Streptomyces* and other actinomycetes and are the most well characterized signaling molecules in these species. A-factor from *Streptomyces griseus* was the first GBL to be characterized, and its identification predates that of the acyl-homoserine lactone quorum-sensing molecules of Gram-negative bacteria (126). The TFR ArpA is the A-factor receptor in *S. griseus* and is part of a large group of closely related TFRs (Fig. 10) that bind GBLs and related signaling molecules such as avenolide from *Streptomyces avermitilis* (127) and the methylenomycin furans from *S. coelicolor* (128). In some cases, such as that of ArpA in *S. griseus*, GBL signaling plays a major role in both antibiotic production and morphological development (9). In other cases, such as that of ScbR and the GBL SCB1 in *S. coelicolor*, some global effects have been noted; however, the predominant role of GBL signaling is in the regulation of a single antibiotic gene cluster (129, 130).

The clustering of all known and predicted GBL receptors in our analysis shows the separate clustering of the so called "pseudo"-GBL receptors and helps to identify putative receptors not associated with GBL biosynthetic enzymes (Fig. 10). Pseudo-GBL receptors such as JadR2 from *S. venezuelae* and ScbR2 from *S. coelicolor* are reported to play a role in the GBL signaling alongside their cognate GBL receptor (i.e., JadR3 [SVEN_5968] and ScbR) by regulating expression of GBL biosynthesis enzymes (131, 132). GBL signaling systems regulate antibiotic biosynthesis, and one report suggests that pseudo-GBL receptors may interact with the final antibiotic product being regulated (133). While the biological relevance of these data is questionable due to the high concentration of antibiotic used in these studies, the idea that pseudo-GBL receptors play a role in GBL signaling pathways is an interesting one.

While the majority of GBL receptors and pseudoreceptors are associated with GBL biosynthetic enzymes, a number of orphan receptors, not associated with biosynthetic gene clusters or resistance genes, have also been identified. Our data provide support for previous reports concerning the role of some of these proteins, namely, CprA and CprB from *S. coelicolor*, in regulating secondary metabolite biosynthesis and morphological differentiation in *Streptomyces* (130, 134). Some bacteria are known to recognize and even metabolize the quorum-sensing signals produced by other bacteria (135). For example, *E. coli* and *Salmonella enterica* do not produce acyl-homoserine lactones but are able to sense them through the receptor SdiA (136). It is tempting to speculate that the role of orphan GBL receptors (e.g., CprA and CprB) and GBL receptors in bacteria not known to produce GBLs (e.g., MSMEG_2193 and MSMEG_2195) may be to recognize GBLs produced by other microbes.

Quorum Sensing

In *Vibrio cholerae*, the TFR HapR plays a major role in quorum-sensing regulation at high cell density (137). HapR orthologs in other species of *Vibrio* include LuxR of *V. harveyi* (not to be confused with transcription factors of the LuxR family such as LuxR of *V. fischeri*) and LitR of *V. fischeri*. The crystal structures of HapR as well as the orthologous SmcR are available (138, 139), and while they both show a putative ligand-binding cavity, none of the

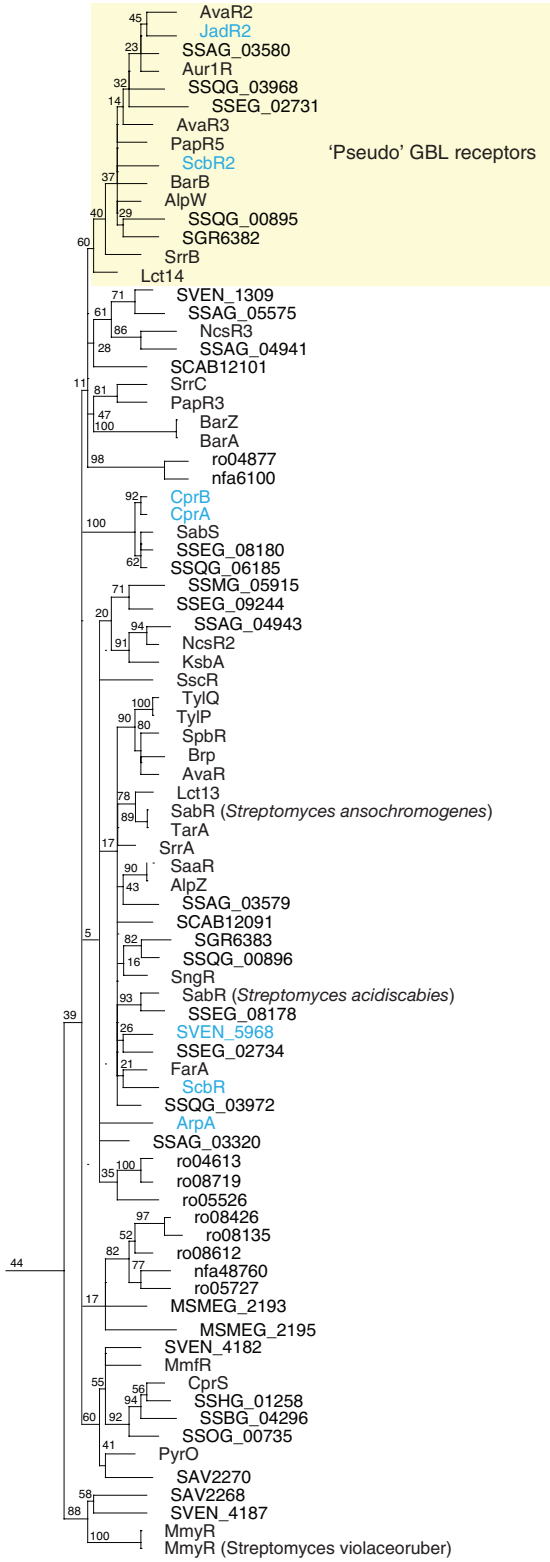

FIG 10 All known TFRs involved in gamma-butyrolactone (GBL) signaling form a single group (data are from reference 25). Within the GBL group, a subclade of TFRs known as the "pseudo"-GBL receptors are highlighted with a yellow box.

known quorum-sensing molecules have been reported to bind these proteins. Instead, expression of HapR is regulated at the posttranscriptional level through interactions of *hapR* mRNA with a number of small RNAs (sRNAs) (140). Recent data indicate an integration of cell density with nutrient availability in quorum sensing (141), raising the possibility that another type of small-molecule signal may serve as a ligand for HapR. The TFR DarR from *M. smegmatis* has been shown to interact with cyclic-di-AMP (142), providing a precedent for interactions between TFRs and second messengers.

TFRs AND CARBON METABOLISM

TFRs have been implicated in both central pathways for carbon metabolism as well as peripheral pathways for the catabolism of specific carbon sources, including the degradation of pollutants and other waste products (e.g., DhaR and MnbR [143, 144]). AcnR in *Corynebacterium glutamicum* controls the expression of the aconitase gene, *acn*. Aconitase is a tricarboxylic acid cycle enzyme that converts citrate to isocitrate and is thought to be an important control point in tricarboxylic acid cycle activity in *Corynebacterium* (145). Structures are available for AcnR (Protein Data Bank [PDB] ID 4AC6, 4ACI, and 4AF5) and show a bound molecule of citrate with evidence for another putative ligand-binding pocket (146). Further studies will be required to determine if AcnR indeed binds multiple small-molecule ligands.

Numerous TFRs have been identified as regulators of the expression of catabolic pathways for different carbon sources. For example, in *Lactococcus lactis*, DhaS regulates the expression of dihydroxyacetone kinase, which is required for glycerol catabolism (69). Unlike the majority of TFRs, DhaS interacts with a protein rather than a small molecule and acts as a transcriptional activator. MdoR from *Mycobacterium* sp. strain JC1 also acts as a transcriptional activator (147). MdoR regulates expression of the *mdo* gene, which is required for oxidation of methanol. The TFRs NicS, PaaR, and RolR are involved in the regulation of metabolism pathways for nicotinic acid, phenyl acetic acid, and resorcinol, respectively (148–150). In each case, the TFR has been shown to interact with the molecule being degraded or a catabolic intermediate.

TFRs AND NITROGEN METABOLISM

AmtR is a master regulator of nitrogen metabolism in *Corynebacterium* (37). The AmtR regulon is composed of at least 33 genes. These encode proteins that import and metabolize different nitrogen sources as well as other regulators of nitrogen metabolism. Unlike most of the characterized TFRs, AmtR interacts with a protein rather than a small-molecule ligand. Consistent with its role in controlling nitrogen assimilation, AmtR interacts with the adenylylated form of GlnK, which accumulates under conditions of nitrogen limitation (67). To date, residues important for this interaction have not been characterized. AmtR homologs are found in *Actinobacteria*, including some species of *Mycobacterium*, *Nocardia*, *Rhodococcus*, and *Streptomyces* (25, 151). In *Streptomyces*, two OmpR-like regulators, GlnR and GlnRII, are the master regulators of nitrogen metabolism (152). Although not present in *Corynebacterium*, GlnR homologs are more conserved in actinobacteria than AmtR homologs; however, there are a few species that encode both (151). *Mycobacterium abscessus*, *Nocardia farcinica*, *Rhodococcus jostii*, *Streptomyces avermitilis*, and *Streptomyces scabies* all encode both AmtR and GlnR homologs. In these species, the genes for the AmtR homologs are divergent to genes involved in the import and degradation of urea (Fig. 11A), suggesting that like AmtR, they may regulate nitrogen metabolism. The gene for another AmtR homolog in *Mycobacterium smegmatis* is located in an operon with genes for a putative enoyl-CoA hydratase and a putative fatty acid-CoA ligase, which do not play an obvious role in nitrogen metabolism. Bioinformatic analysis suggests that mycobacteria contain putative GlnR-binding sites throughout their chromosomes, while AmtR-binding sites in strains encoding AmtR homologs were not identified (151). It is tempting to speculate that in strains encoding both GlnR and AmtR homologs, AmtR may function as a local rather than a global repressor.

In *E. coli*, RutR is the master regulator of pyrimidine metabolism. RutR regulates transcription of the divergently transcribed *rut* operon, encoding gene products involved in the degradation of pyrimidines for use as a nitrogen source. RutR also regulates a number of other targets located elsewhere on the chromosome, including the *carAB*, *gadAX*, *gadBC*, *ygiF-glnE*, and *gcl-hyi-glxR* operons, which are involved in various aspects of pyrimidine and glutamate metabolism (153). A homolog of RutR, PydR, has been identified as the regulator of genes required for pyrimidine degradation via the reductive pathway in *Pseudomonas putida* (154). A crystal structure is available for RutR in complex with its inducing ligand uracil (155). Residues involved in uracil binding are conserved in PydR, indicating that PydR may also be a uracil-responsive transcription factor (154). Our analysis shows separate RutR and PydR subclades within a larger group of TFRs probably involved in the metabolism of pyrimidines as well as possibly purines (Fig. 11B). *P. aeruginosa* encodes four RutR-PydR homologs, and based on genomic context, all four homologs are likely to play a role in nucleotide metabolism. This RutR-PydR group serves as an example of how very similar TFRs may regulate different pathways involved in the same overall physiological process, in this case nucleotide metabolism. Another example of this is the involvement of FabR and DesT in regulating fatty acid saturation in *E. coli* and *P. aeruginosa*, respectively (see TFRs and Lipid Metabolism below).

XdhR from *S. coelicolor* regulates the expression of the divergently transcribed four-gene operon encoding the subunits of, and a maturation factor for, xanthine dehydrogenase. Xanthine dehydrogenase activity is responsible for the conversion of xanthine to uric acid, which can be broken down and used as a nitrogen source. XdhR may therefore provide a link between primary metabolism, morphological development, and antibiotic production in *Streptomyces* (156), and our analysis shows that XdhR is indeed well conserved in this genus. The potato pathogen *Streptomyces scabies* carries two *xdhR* homologs (Fig. 11C). SCAB82081 encodes an ortholog of XdhR, while the role of SCAB83171 is unclear. We have also identified XdhR homologs in a number of Gram-negative bacteria (e.g., *Pseudomonas putida* and *Rahnella*). These XdhR homologs are predicted to regulate a putative short-chain dehydrogenase of unknown function. Given the phylogenetic grouping, these XdhR homologs and the short-chain dehydrogenases they regulate should be investigated for a role in purine metabolism.

TFRs AND LIPID METABOLISM

There are numerous parallels between the biosyntheses of polyketide antibiotics and fatty acids. We have noted above the

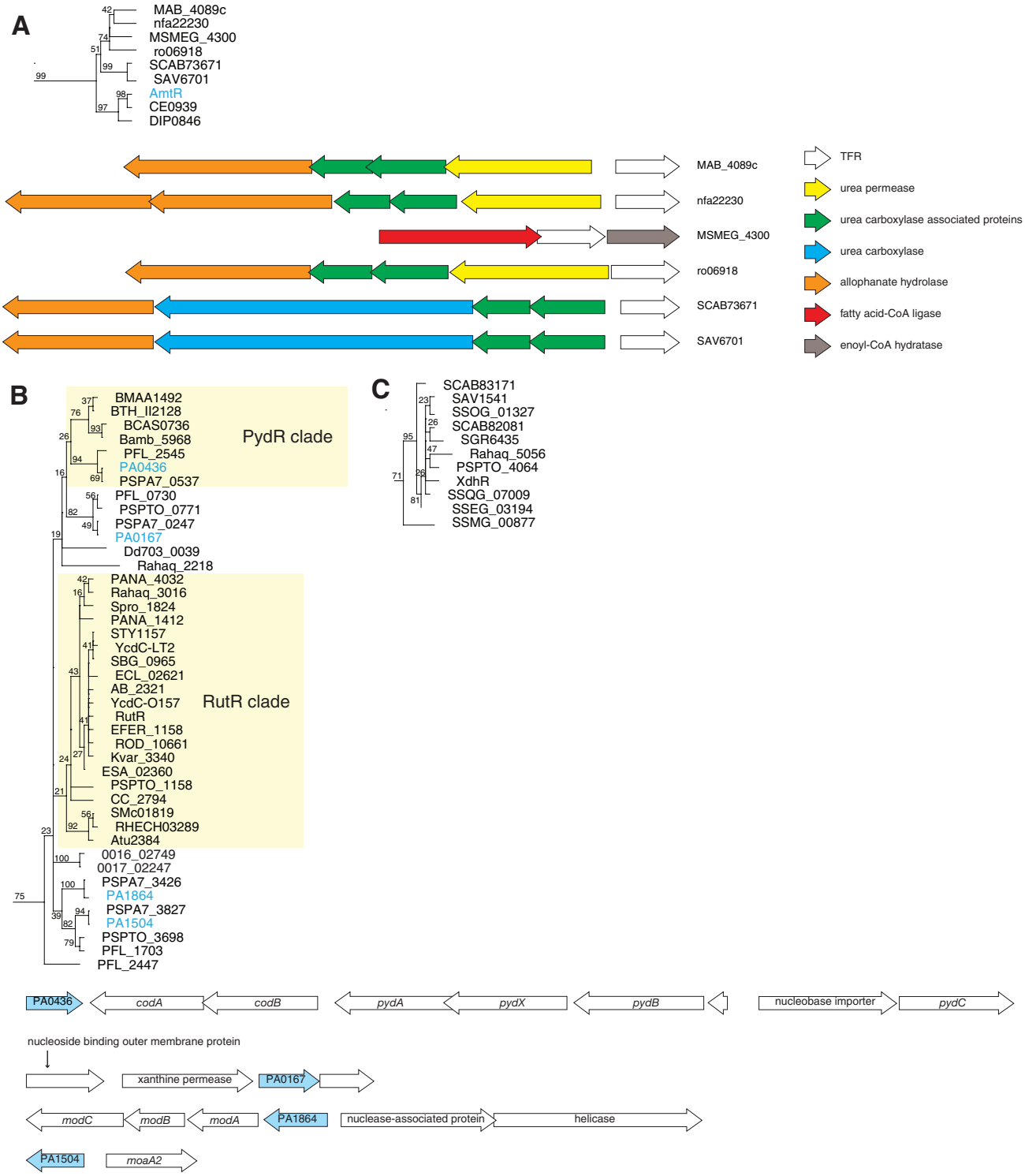

FIG 11 TFRs involved in nitrogen metabolism. (A) Homologs of AmtR, a global regulator of nitrogen metabolism in *Corynebacterium*, may act as local regulators in related organisms. (B) RutR and PydR homologs from separate clades within a larger group of TFRs predicted to be involved in nucleotide metabolism. (C) Homologs of XdhR may be involved in purine metabolism. (Adapted from reference 25.)

involvement of TFRs in regulating resistance to numerous polyketide antibiotics, including tetracycline. TFRs also play a major role in regulating fatty acid metabolism as well as the metabolism of other lipid compounds, including sterols.

Fatty Acid Biosynthesis and Degradation

FasR from *C. glutamicum* is a regulator of lipid biosynthesis. In a *fasR* mutant, 17 genes were differentially expressed, including

fasA, *fasB*, *accB*, *accC*, and *accD1* (157). In addition, two other TFRs were found to be differentially expressed in the *fasR* mutant, one of which, Clg1640, may also play a role in fatty acid metabolism. Clg1640 is found in a group with FadR from *Pseudonocardia autotropica* (Fig. 12A). In *P. autotropica*, FadR controls an operon involved in fatty acid degradation (158). Also located in this group are the AtrA homologs from *Streptomyces*. AtrA is a pleiotropic regulator of antibiotic production in *Streptomyces* (6). The inducing ligand for AtrA is unknown, but given its grouping with two TFRs involved in fatty acid metabolism, a fatty acid derivative should be investigated. Transcriptomics studies support a role for AveI, the AtrA ortholog of *Streptomyces avermitilis*, in the regulation of carbon flux toward antibiotic production. Indeed, genes involved in fatty acid metabolism were downregulated in an *aveI* mutant (159). FasR itself is located in a group with another known regulator of antibiotic production in *S. coelicolor*, SCO1712 (160) (Fig. 12B), further highlighting a connection between fatty acid metabolism and antibiotic production. It is worth highlighting that AtrA acts as a transcriptional activator, in contrast to the role of most TFRs as repressors (6).

While FasR is currently the only known TFR involved in fatty acid biosynthesis, numerous TFRs are known to play a role in fatty acid degradation. In addition to FadR from *P. autotropica* (see above), two other TFRs have been called FadR. FadR from *B. subtilis* regulates five operons required for fatty acid degradation and recognizes long-chain fatty acyl-CoAs (161). FadR from *Thermus thermophilus* controls the expression of numerous genes implicated in fatty acid degradation (57). Although there are currently three TFRs bearing the name FadR, none grouped together in our analysis (25). While the available data support a role for all three TFRs in fatty acid degradation, the above proteins are clearly not orthologous.

In *M. tuberculosis*, at least two TFRs are known to play a role in lipid metabolism, Fad35R and Mce3R. Fad35R controls the expression of an acyl-CoA synthetase encoded by Fad35 in response to fatty acid derivatives (162). Mce3R represses the transcription of the virulence-related *mce3* locus as well as other genes required for fatty acid degradation. Mce3R is among a group of TFRs containing duplicated TFR domains within a single peptide. Our analysis has shown that the N- and C-terminal TFR domains form separate clusters within the same group (Fig. 12C). This indicates that the N-terminal domains are more similar to each other than they are to the C-terminal domains, and this group of TFRs may be the result of a single duplication and gene fusion event. Although the inducing ligand for Mce3R has not been identified, it is located within a larger group with Fad35R (Fig. 12C), indicating that it may likewise be induced by a fatty acid derivative.

PsrA from *P. aeruginosa* responds to long-chain fatty acids to control expression of *fad* genes (163). In addition, PsrA plays a role in resistance to cationic antimicrobial peptides, antibiotic production, quorum sensing, and virulence, indicating that PsrA and long-chain fatty acids play an important role in the physiology of this important opportunistic pathogen.

Lipid Saturation

As mentioned above, FabR from *E. coli* and DesT from *P. aeruginosa* regulate different pathways involved in the same overall physiological process, in this case fatty acid saturation. Our phylogenetic analysis shows that they are located in the same group (25) (Fig. 12D). FabR regulates the expression of *fabA* and *fabB*, which are required for the synthesis of unsaturated fatty acids (164). The genes encoding FabA, FabB, and FabR are all located in different areas of the chromosome, and unlike most TFRs, FabR is not autoregulatory (165). While not essential for DNA binding by FabR, unsaturated thioesters (i.e., acyl-ACP or acyl-CoA) were found to enhance binding, while the FabR-DNA interaction was disrupted in the presence of saturated thioesters (165). DesT shows a similar pattern of ligand binding, where DNA binding is enhanced by unsaturated acyl-CoAs and disrupted by saturated acyl-CoAs (166). DesT regulates the expression of *desC* and *desB*, which are divergently transcribed from *desT* (166). The *desC* and *desB* genes encode a reductase and an acyl-CoA desaturase, respectively. Whereas FabR regulates the biosynthesis of unsaturated fatty acids, DesT regulates gene products required for the desaturation of preformed acyl chains.

Synthesis and Degradation of Storage Polymers

In *Pseudomonas putida*, PhaD controls the expression of genes involved in polyhydroxyalkanoate (PHA) metabolism (167). PHAs are produced as carbon storage granules and are being investigated for their potential as alternative plastics (168). PHA polymers are synthesized from (*R*)-3-hydroxyacyl-CoA, which can be produced from various intermediates of fatty acid degradation. Although not experimentally demonstrated, PhaD is thought to bind a fatty acyl-CoA intermediate of β oxidation (167). Interestingly, PhaD is located in a larger group with NGO0393 and NMB0810 from *Neisseria gonorrhoeae* and *Neisseria meningitidis*, respectively (Fig. 12E). The NGO0393 and NMB0810 orthologs are one of only two TFRs encoded by each species. The roles of NGO0393 and NMB0810 in the metabolism of storage polymers have not been investigated.

Terpene Utilization

Terpenes, including cholesterol, are an important class of natural product built from isoprene units. Two TFRs, KstR and KstR2, control cholesterol degradation in *M. tuberculosis* (169–172). The genes in the KstR and KstR2 regulons are known to be upregulated *in vivo* and are important for virulence of *M. tuberculosis* (173). Specific inducing ligands for KstR and KstR2 have not been identified. Although KstR and KstR2 are located in separate groups (Fig. 12F and G), other TFRs in both groups further suggest a role in terpene metabolism. For example, Rv0767c is in the same group as KstR and is located in an operon with Rv0764c, encoding a putative steroid demethylase. KstR2 is in a group with AtuR from *P. aeruginosa*. AtuR controls the expression of genes required for acyclic terpene utilization (174). A number of TFRs (CampR, CmtI, CmtR, CymR, and PsbI) that control the utilization of cyclic terpenes such as camphor and *p*-cymene have also been identified (175–179).

TFRs AND AMINO ACID METABOLISM

Three TFRs, AguR, LiuQ, and McbR, are involved in regulating amino acid metabolism. While AguR and LiuQ act as local regulators controlling the expression of adjacent genes involved in amino acid degradation, McbR acts as a global regulator for sulfur metabolism.

Agmatine is an intermediate in the arginine decarboxylase (ADC) pathway for arginine degradation (180). In *P. aeruginosa* PAO1, the TFR AguR controls expression of the *aguAB* operon, involved in agmatine utilization, and is induced by agmatine

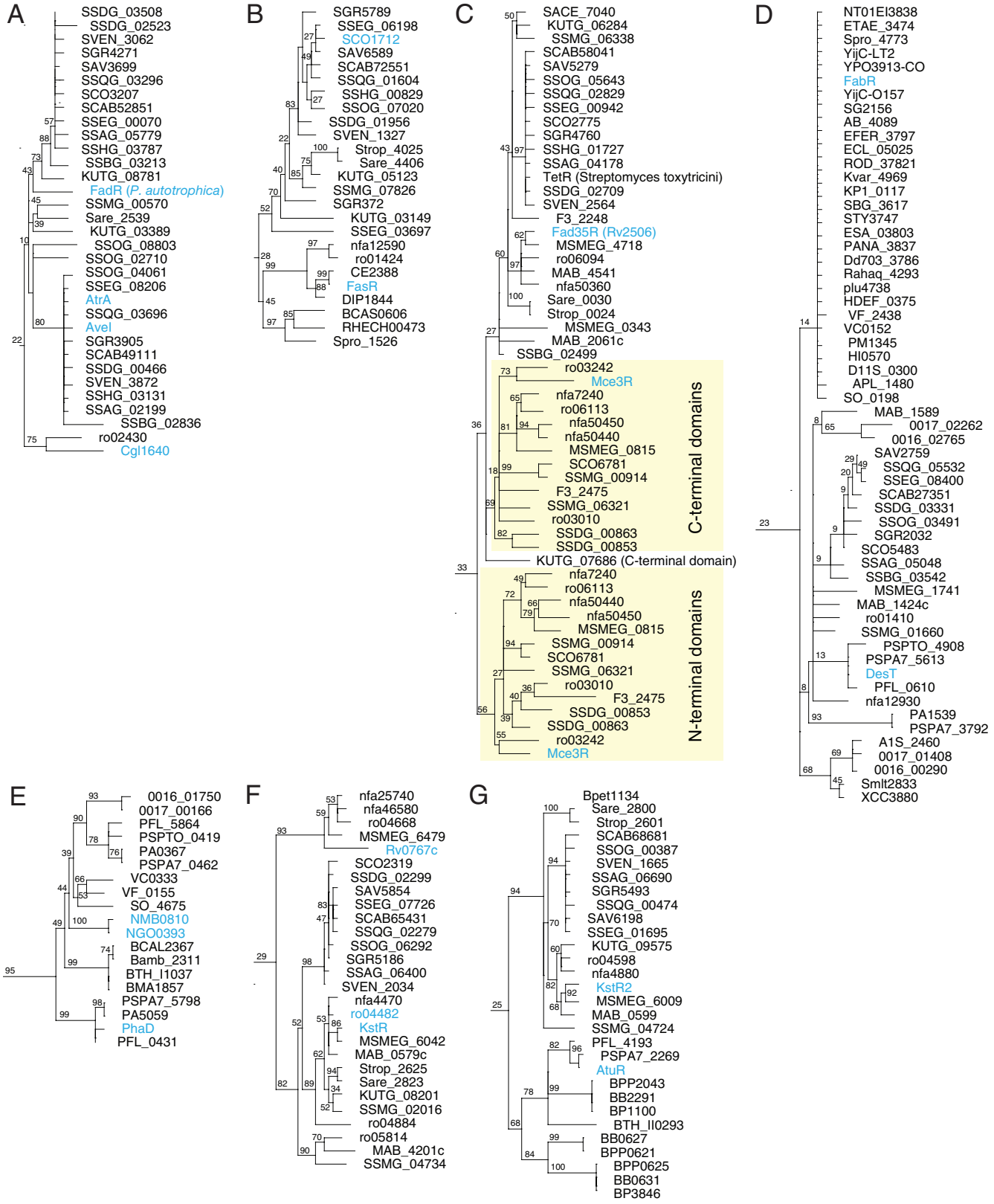

FIG 12 TFRs involved in lipid metabolism. TFRs involved in lipid metabolism are found in many groups. (A to C) TFRs involved in fatty acid biosynthesis and degradation. (D) TFRs regulating fatty acid saturation. (E) TFRs involved in the synthesis and degradation of storage polymers. (F and G) TFRs involved in terpene utilization. (Adapted from reference 25.)

(181). AguR is conserved in many members of the genus *Pseudomonas* but is absent from *P. aeruginosa* PA14, where an alternative operon for agmatine metabolism also plays a role in biofilm formation (182).

The TFR LiuQ has been identified using comparative genomics as the regulator of the *liuABCD* genes, required for the degradation of branched-chain amino acids in *Burkholderiales* (183). Although DNA binding was not experimentally tested, a putative LiuQ binding site was identified.

McbR from *C. glutamicum* is a global regulator of sulfur metabolism, including the genes required for the biosynthesis of sulfur-containing amino acids (184, 185). DNA binding by McbR is modulated by the small molecule *S*-adenosylhomocysteine, a byproduct of methylation reactions (185). Deletion of *mcbR* causes numerous pleiotropic effects on additional aspects of growth and metabolism, indicating that McbR plays a central role in regulating numerous physiological processes in *C. glutamicum* (186).

TFRs AND COFACTOR METABOLISM

Biotin

In many bacteria, BirA controls the expression of biotin biosynthesis genes (187). BirA is a bifunctional protein acting as the biotin-protein ligase as well as a transcriptional regulator. In some organisms, BirA lacks the transcriptional regulatory domain and the biotin biosynthesis genes are controlled by other transcription factors. In alphaproteobacteria, the GntR family regulator BioR controls the expression of biotin biosynthesis genes (188), while in *Corynebacterium* and certain related actinobacteria, the TFR BioQ is the regulator of biotin biosynthesis (189). BioQ interacts with a 13-bp palindromic region upstream of a number of biotin biosynthesis genes. Biotin itself was not found to disrupt the BioQ-DNA interaction *in vitro*, but this does not rule out the possibility of a biotin intermediate serving as a ligand for BioQ.

Heme

Two TFRs, HrtR from *Lactococcus lactis* and HemR from *Propionibacterium freudenreichii*, have been implicated in heme homeostasis. HemR is a putative regulator of genes required for the conversion of glutamate to protoheme in *P. freudenreichii*. It is transcribed divergently from *hemX*, encoding a putative heme transporter. The details of HemR DNA binding and ligand binding have not been investigated (190). *L. lactis* does not synthesize heme. HrtR senses intracellular heme and regulates expression of a heme exporter encoded by HrtBA (191).

TFRs AND CELL DIVISION

SlmA from *E. coli* binds and antagonizes polymerization of the bacterial tubulin homolog FtsZ, preventing cell division from occurring over the chromosome, in a process known as nucleoid occlusion (68, 192, 193). SlmA is not known to interact with a small molecule but rather interacts directly with the tubulin-like cell division protein FtsZ. This interaction is believed to be important for preventing the formation of cell division septa around unsegregated chromosomes. In one model for SlmA function (70), the FtsZ interaction interface on SlmA is completely exposed only when SlmA is bound to DNA. Hence SlmA affect FtsZ polymerization only in areas where DNA is present.

Based on our analysis (25), SlmA homologs are found in most members of the gamma- and betaproteobacteria. Exceptions in which this mechanism appears to be absent include *Acinetobacter*, *Francisella*, *Legionella*, *Pseudomonas*, *Stenotrophomonas*, *Xanthomonas*, and *Neisseria*. A possible SlmA ortholog in *Bordetella parapertussis* was found to be the product of a pseudogene. In *E. coli*, the absence of both the Min system, also involved in regulating FtsZ function, and SlmA results in a synthetic lethal phenotype (68). How FtsZ ring placement is regulated in Gram-negative bacteria such as *Myxococcus*, *Campylobacter*, and *Bacteroides* where both the Min system and SlmA are absent is unknown, but evidence suggests that there are as yet-unidentified factors involved in nucleoid occlusion (194).

In *Bacillus*, Noc, a protein unrelated to SlmA, controls nucleoid occlusion. Noc is a homolog of ParB chromosome-partitioning proteins. The TFR RefZ, however, is involved in regulating the transition from medial to polar cell division during sporulation, possibly as a direct effector of FtsZ polymerization (195). Our analysis does not indicate a close relationship between SlmA and RefZ.

FUTURE DIRECTIONS AND CHALLENGES

TFRs play an important role in regulating numerous aspects of bacterial physiology. Through genomics and structural studies, we have learned a great deal regarding the types of gene products regulated by TFRs and the mechanisms by which TFRs interact with both DNA and small molecules. Although genomics allows us to predict the target genes for the majority of TFRs, this cannot be done for type III TFRs, and other methodologies must be employed. Different models still exist as to the structural changes that TFRs undergo upon ligand binding and the precise molecular mechanisms behind derepression, and future NMR studies may help to resolve discrepancies in the current data. Determination of the identities of the small-molecule ligands, or other interacting partners, bound by the more than 200,000 TFRs in the public databases probably represents the most understudied and challenging area of TFR biology, and future work will be required to identify these ligands.

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REFERENCES

1. **Laub MT, Goulian M.** 2007. Specificity in two-component signal transduction pathways. Annu. Rev. Genet. **41:**121–145.
2. **Ulrich LE, Koonin EV, Zhulin IB.** 2005. One-component systems dominate signal transduction in prokaryotes. Trends Microbiol. **13:**52–56.
3. **Schreiter ER, Drennan CL.** 2007. Ribbon-helix-helix transcription factors: variations on a theme. Nat. Rev. Microbiol. **5:**710–720.
4. **Pérez-Rueda E, Collado-Vides J.** 2000. The repertoire of DNA-binding transcriptional regulators in *Escherichia coli* K-12. Nucleic Acids Res. **28:**1838–1847.
5. **Pérez-Rueda E, Collado-Vides J.** 2001. Common history at the origin of the position-function correlation in transcriptional regulators in archaea and bacteria. J. Mol. Evol. **53:**172–179.
6. **Uguru GC, Stephens KE, Stead JA, Towle JE, Baumberg S, McDowall KJ.** 2005. Transcriptional activation of the pathway-specific regulator of the actinorhodin biosynthetic genes in *Streptomyces coelicolor*. Mol. Microbiol. **58:**131–150.
7. **Schleif R.** 2010. AraC protein, regulation of the L-arabinose operon in

Escherichia coli, and the light switch mechanism of AraC action. FEMS Microbiol. Rev. **34:**779–796.
8. **Joshi MV, Bignell DR, Johnson EG, Sparks JP, Gibson DM, Loria R.** 2007. The AraC/XylS regulator TxtR modulates thaxtomin biosynthesis and virulence in *Streptomyces scabies*. Mol. Microbiol. **66:**633–642.
9. **McCormick JR, Flärdh K.** 2012. Signals and regulators that govern *Streptomyces* development. FEMS Microbiol. Rev. **36:**206–231.
10. **Yang J, Tauschek M, Robins-Browne RM.** 2011. Control of bacterial virulence by AraC-like regulators that respond to chemical signals. Trends Microbiol. **19:**128–135.
11. **Makarova KS, Wolf YI, Koonin EV.** 2009. Comprehensive comparative-genomic analysis of type 2 toxin-antitoxin systems and related mobile stress response systems in prokaryotes. Biol. Direct **4:**19.
12. **McEwan AG, Djoko KY, Chen NH, Couñago RL, Kidd SP, Potter AJ, Jennings MP.** 2011. Novel bacterial MerR-like regulators their role in the response to carbonyl and nitrosative stress. Adv. Microb. Physiol. **58:**1–22.
13. **Deng W, Li C, Xie J.** 2013. The underling mechanism of bacterial TetR/AcrR family transcriptional repressors. Cell Signal. **25:**1608–1613.
14. **Ramos JL, Martínez-Bueno M, Molina-Henares AJ, Terán W, Watanabe K, Zhang X, Gallegos MT, Brennan R, Tobes R.** 2005. The TetR family of transcriptional repressors. Microbiol. Mol. Biol. Rev. **69:**326–356.
15. **Izaki K, Kiuchi K, Arima K.** 1966. Specificity and mechanism of tetracycline resistance in a multiple drug resistant strain of *Escherichia coli*. J. Bacteriol. **91:**628–633.
16. **Yang HL, Zubay G, Levy SB.** 1976. Synthesis of an R plasmid protein associated with tetracycline resistance is negatively regulated. Proc. Natl. Acad. Sci. U. S. A. **73:**1509–1512.
17. **Beck CF, Mutzel R, Barbé J, Müller W.** 1982. A multifunctional gene (*tetR*) controls Tn*10*-encoded tetracycline resistance. J. Bacteriol. **150:**633–642.
18. **Bertrand KP, Postle K, Wray LV, Reznikoff WS.** 1983. Overlapping divergent promoters control expression of Tn10 tetracycline resistance. Gene **23:**149–156.
19. **Postle K, Nguyen TT, Bertrand KP.** 1984. Nucleotide sequence of the repressor gene of the Tn10 tetracycline resistance determinant. Nucleic Acids Res. **12:**4849–4863.
20. **Wray LV, Jorgensen RA, Reznikoff WS.** 1981. Identification of the tetracycline resistance promoter and repressor in transposon Tn*10*. J. Bacteriol. **147:**297–304.
21. **Zupancic TJ, King SR, Pogue-Geile KL, Jaskunas SR.** 1980. Identification of a second tetracycline-inducible polypeptide encoded by Tn*10*. J. Bacteriol. **144:**346–355.
22. **Kisker C, Hinrichs W, Tovar K, Hillen W, Saenger W.** 1995. The complex formed between Tet repressor and tetracycline-Mg^{2+} reveals mechanism of antibiotic resistance. J. Mol. Biol. **247:**260–280.
23. **Ahn SK, Cuthbertson L, Nodwell JR.** 2012. Genome context as a predictive tool for identifying regulatory targets of the TetR family transcriptional regulators. PLoS One **7:**e50562. doi:10.1371/journal.pone.0050562.
24. **Yu Z, Reichheld SE, Savchenko A, Parkinson J, Davidson AR.** 2010. A comprehensive analysis of structural and sequence conservation in the TetR family transcriptional regulators. J. Mol. Biol. **400:**847–864.
25. **Cuthbertson L, Ahn SK, Nodwell JR.** 2013. Deglycosylation as a mechanism of inducible antibiotic resistance revealed using a global relational tree for one-component regulators. Chem. Biol. **20:**232–240.
26. **Bentley SD, Chater KF, Cerdeño-Tárraga AM, Challis GL, Thomson NR, James KD, Harris DE, Quail MA, Kieser H, Harper D, Bateman A, Brown S, Chandra G, Chen CW, Collins M, Cronin A, Fraser A, Goble A, Hidalgo J, Hornsby T, Howarth S, Huang CH, Kieser T, Larke L, Murphy L, Oliver K, O'Neil S, Rabbinowitsch E, Rajandream MA, Rutherford K, Rutter S, Seeger K, Saunders D, Sharp S, Squares R, Squares S, Taylor K, Warren T, Wietzorrek A, Woodward J, Barrell BG, Parkhill J, Hopwood DA.** 2002. Complete genome sequence of the model actinomycete *Streptomyces coelicolor* A3(2). Nature **417:**141–147.
27. **Ishihama A.** 2010. Prokaryotic genome regulation: multifactor promoters, multitarget regulators and hierarchic networks. FEMS Microbiol. Rev. **34:**628–645.
28. **Ma Q, Yang Z, Pu M, Peti W, Wood TK.** 2011. Engineering a novel c-di-GMP-binding protein for biofilm dispersal. Environ. Microbiol. **13:**631–642.
29. **Partridge JD, Bodenmiller DM, Humphrys MS, Spiro S.** 2009. NsrR targets in the *Escherichia coli* genome: new insights into DNA sequence requirements for binding and a role for NsrR in the regulation of motility. Mol. Microbiol. **73:**680–694.
30. **Roy PH, Tetu SG, Larouche A, Elbourne L, Tremblay S, Ren Q, Dodson R, Harkins D, Shay R, Watkins K, Mahamoud Y, Paulsen IT.** 2010. Complete genome sequence of the multiresistant taxonomic outlier *Pseudomonas aeruginosa* PA7. PLoS One **5:**e8842. doi:10.1371/journal.pone.0008842.
31. **Yamamoto M, Ueda A, Kudo M, Matsuo Y, Fukushima J, Nakae T, Kaneko T, Ishigatsubo Y.** 2009. Role of MexZ and PA5471 in transcriptional regulation of mexXY in *Pseudomonas aeruginosa*. Microbiology **155:**3312–3321.
32. **Feliziani S, Luján AM, Moyano AJ, Sola C, Bocco JL, Montanaro P, Canigia LF, Argaraña CE, Smania AM.** 2010. Mucoidy, quorum sensing, mismatch repair and antibiotic resistance in *Pseudomonas aeruginosa* from cystic fibrosis chronic airways infections. PLoS One **5:**e12669. doi:10.1371/journal.pone.0012669.
33. **Wei Q, Tarighi S, A Dötsch, S Häussler, M Müsken, Wright VJ, M Cámara, Williams P, Haenen S, Boerjan B, Bogaerts A, Vierstraete E, Verleyen P, Schoofs L, Willaert R, De Groote VN, Michiels J, Vercammen K, Crabbé A, Cornelis P.** 2011. Phenotypic and genome-wide analysis of an antibiotic-resistant small colony variant (SCV) of *Pseudomonas aeruginosa*. PLoS One **6:**e29276. doi:10.1371/journal.pone.0029276.
34. **Morita Y, Cao L, Gould VC, Avison MB, Poole K.** 2006. *nalD* encodes a second repressor of the *mexAB-oprM* multidrug efflux operon of *Pseudomonas aeruginosa*. J. Bacteriol. **188:**8649–8654.
35. **Yang YH, Kim JN, Song E, Kim E, Oh MK, Kim BG.** 2008. Finding new pathway-specific regulators by clustering method using threshold standard deviation based on DNA chip data of *Streptomyces coelicolor*. Appl. Microbiol. Biotechnol. **80:**709–717.
36. **Hasselt K, Rankl S, Worsch S, Burkovski A.** 2011. Adaptation of AmtR-controlled gene expression by modulation of AmtR binding activity in *Corynebacterium glutamicum*. J. Biotechnol. **154:**156–162.
37. **Jakoby M, Nolden L, Meier-Wagner J, Krämer R, Burkovski A.** 2000. AmtR, a global repressor in the nitrogen regulation system of *Corynebacterium glutamicum*. Mol. Microbiol. **37:**964–977.
38. **Muhl D, Jessberger N, Hasselt K, Jardin C, Sticht H, Burkovski A.** 2009. DNA binding by *Corynebacterium glutamicum* TetR-type transcription regulator AmtR. BMC Mol. Biol. **10:**73.
39. **Cerda-Maira FA, Ringelberg CS, Taylor RK.** 2008. The bile response repressor BreR regulates expression of the *Vibrio cholerae breAB* efflux system operon. J. Bacteriol. **190:**7441–7452.
40. **Quiñones B, Pujol CJ, Lindow SE.** 2004. Regulation of AHL production and its contribution to epiphytic fitness in *Pseudomonas syringae*. Mol. Plant Microbe Interact. **17:**521–531.
41. **Mitchell G, Gattuso M, Grondin G, Marsault É Bouarab K, Malouin F.** 2011. Tomatidine inhibits replication of *Staphylococcus aureus* small-colony variants in cystic fibrosis airway epithelial cells. Antimicrob. Agents Chemother. **55:**1937–1945.
42. **Le TB, Stevenson CE, Fiedler HP, Maxwell A, Lawson DM, Buttner MJ.** 2011. Structures of the TetR-like simocyclinone efflux pump repressor, SimR, and the mechanism of ligand-mediated derepression. J. Mol. Biol. **408:**40–56.
43. **Itou H, Okada U, Suzuki H, Yao M, Wachi M, Watanabe N, Tanaka I.** 2005. The CGL2612 protein from *Corynebacterium glutamicum* is a drug resistance-related transcriptional repressor: structural and functional analysis of a newly identified transcription factor from genomic DNA analysis. J. Biol. Chem. **280:**38711–38719.
44. **Miller DJ, Zhang YM, Subramanian C, Rock CO, White SW.** 2010. Structural basis for the transcriptional regulation of membrane lipid homeostasis. Nat. Struct. Mol. Biol. **17:**971–975.
45. **Orth P, Schnappinger D, Hillen W, Saenger W, Hinrichs W.** 2000. Structural basis of gene regulation by the tetracycline inducible Tet repressor-operator system. Nat. Struct. Biol. **7:**215–219.
46. **Sawai H, Yamanaka M, Sugimoto H, Shiro Y, Aono S.** 2012. Structural basis for the transcriptional regulation of heme homeostasis in *Lactococcus lactis*. J. Biol. Chem. **287:**30755–30768.
47. **Schumacher MA, Miller MC, Grkovic S, Brown MH, Skurray RA, Brennan RG.** 2002. Structural basis for cooperative DNA binding by two dimers of the multidrug-binding protein QacR. EMBO. J. **21:**1210–1218.
48. **Hochschild A, Lewis M.** 2009. The bacteriophage lambda CI protein finds an asymmetric solution. Curr. Opin. Struct. Biol. **19:**79–86.

49. **Li DF, Zhang N, Hou YJ, Huang Y, Hu Y, Zhang Y, Liu SJ, Wang DC.** 2011. Crystal structures of the transcriptional repressor RolR reveals a novel recognition mechanism between inducer and regulator. PLoS One **6:**e19529. doi:10.1371/journal.pone.0019529.
50. **Le TB, Fiedler HP, den Hengst CD, Ahn SK, Maxwell A, Buttner MJ.** 2009. Coupling of the biosynthesis and export of the DNA gyrase inhibitor simocyclinone in *Streptomyces antibioticus*. Mol. Microbiol. **72:** 1462–1474.
51. **Alguel Y, Meng C, Terán W, Krell T, Ramos JL, Gallegos MT, Zhang X.** 2007. Crystal structures of multidrug binding protein TtgR in complex with antibiotics and plant antimicrobials. J. Mol. Biol. **369:**829–840.
52. **Hernández A, Maté MJ, Sánchez-Díaz PC, Romero A, Rojo F, Martínez JL.** 2009. Structural and functional analysis of SmeT, the repressor of the *Stenotrophomonas maltophilia* multidrug efflux pump SmeDEF. J. Biol. Chem. **284:**14428–14438.
53. **Schumacher MA, Miller MC, Grkovic S, Brown MH, Skurray RA, Brennan RG.** 2001. Structural mechanisms of QacR induction and multidrug recognition. Science **294:**2158–2163.
54. **Willems AR, Tahlan K, Taguchi T, Zhang K, Lee ZZ, Ichinose K, Junop MS, Nodwell JR.** 2008. Crystal structures of the *Streptomyces coelicolor* TetR-like protein ActR alone and in complex with actinorhodin or the actinorhodin biosynthetic precursor (S)-DNPA. J. Mol. Biol. **376:**1377–1387.
55. **Bellinzoni M, Buroni S, Schaeffer F, Riccardi G, De Rossi E, Alzari PM.** 2009. Structural plasticity and distinct drug-binding modes of LfrR, a mycobacterial efflux pump regulator. J. Bacteriol. **191:**7531–7537.
56. **Lei HT, Shen Z, Surana P, Routh MD, Su CC, Zhang Q, Yu EW.** 2011. Crystal structures of CmeR-bile acid complexes from *Campylobacter jejuni*. Protein Sci. **20:**712–723.
57. **Agari Y, Agari K, Sakamoto K, Kuramitsu S, Shinkai A.** 2011. TetR-family transcriptional repressor *Thermus thermophilus* FadR controls fatty acid degradation. Microbiology **157:**1589–1601.
58. **Frénois F, Engohang-Ndong J, Locht C, Baulard AR, Villeret V.** 2004. Structure of EthR in a ligand bound conformation reveals therapeutic perspectives against tuberculosis. Mol. Cell **16:**301–307.
59. **Zheng J, Sagar V, Smolinsky A, Bourke C, LaRonde-LeBlanc N, Cropp TA.** 2009. Structure and function of the macrolide biosensor protein, MphR(A), with and without erythromycin. J. Mol. Biol. **387:**1250–1260.
60. **Grkovic S, Hardie KM, Brown MH, Skurray RA.** 2003. Interactions of the QacR multidrug-binding protein with structurally diverse ligands: implications for the evolution of the binding pocket. Biochemistry **42:** 15226–15236.
61. **Hernández A, Ruiz FM, Romero A, Martínez JL.** 2011. The binding of triclosan to SmeT, the repressor of the multidrug efflux pump SmeDEF, induces antibiotic resistance in *Stenotrophomonas maltophilia*. PLoS Pathog. **7:**e1002103. doi:10.1371/journal.ppat.1002103.
62. **Dover LG, Corsino PE, Daniels IR, Cocklin SL, Tatituri V, Besra GS, Fütterer K.** 2004. Crystal structure of the TetR/CamR family repressor *Mycobacterium tuberculosis* EthR implicated in ethionamide resistance. J. Mol. Biol. **340:**1095–1105.
63. **Flipo M, Willand N, Lecat-Guillet N, Hounsou C, Desroses M, Leroux F, Lens Z, Villeret V, Wohlkönig A, Wintjens R, Christophe T, Kyoung Jeon H, Locht C, Brodin P, Baulard AR, Déprez B.** 2012. Discovery of novel N-phenylphenoxyacetamide derivatives as EthR inhibitors and ethionamide boosters by combining high-throughput screening and synthesis. J. Med. Chem. **55:**6391–6402.
64. **Willand N, Dirié B, Carette X, Bifani P, Singhal A, Desroses M, Leroux F, Willery E, Mathys V, R Déprez-Poulain, Delcroix G, Frénois F, Aumercier M, Locht C, Villeret V, B Déprez, Baulard AR.** 2009. Synthetic EthR inhibitors boost antituberculous activity of ethionamide. Nat. Med. **15:**537–544.
65. **Willand N, Desroses M, Toto P, Dirié B, Lens Z, Villeret V, Rucktooa P, Locht C, Baulard A, Deprez B.** 2010. Exploring drug target flexibility using in situ click chemistry: application to a mycobacterial transcriptional regulator. ACS Chem. Biol. **5:**1007–1013.
66. **Carette X, Blondiaux N, Willery E, Hoos S, Lecat-Guillet N, Lens Z, Wohlkönig A, Wintjens R, Soror SH, Frénois F, Dirié B, Villeret V, England P, Lippens G, Deprez B, Locht C, Willand N, Baulard AR.** 2012. Structural activation of the transcriptional repressor EthR from *Mycobacterium tuberculosis* by single amino acid change mimicking natural and synthetic ligands. Nucleic Acids Res. **40:**3018–3030.
67. **Beckers G, Strösser J, Hildebrandt U, Kalinowski J, Farwick M, Krämer R, Burkovski A.** 2005. Regulation of AmtR-controlled gene expression in *Corynebacterium glutamicum*: mechanism and characterization of the AmtR regulon. Mol. Microbiol. **58:**580–595.
68. **Bernhardt TG, de Boer PA.** 2005. SlmA, a nucleoid-associated, FtsZ binding protein required for blocking septal ring assembly over chromosomes in *E. coli*. Mol. Cell **18:**555–564.
69. **Christen S, Srinivas A, Bähler P, Zeller A, Pridmore D, Bieniossek C, Baumann U, Erni B.** 2006. Regulation of the *dha* operon of *Lactococcus lactis*: a deviation from the rule followed by the TetR family of transcription regulators. J. Biol. Chem. **281:**23129–23137.
70. **Cho H, Bernhardt TG.** 2013. Identification of the SlmA active site responsible for blocking bacterial cytokinetic ring assembly over the chromosome. PLoS Genet. **9:**e1003304. doi:10.1371/journal.pgen.1003304.
71. **Kloosterman TG, van der Kooi-Pol MM, Bijlsma JJ, Kuipers OP.** 2007. The novel transcriptional regulator SczA mediates protection against Zn^{2+} stress by activation of the Zn^{2+}-resistance gene *czcD* in *Streptococcus pneumoniae*. Mol. Microbiol. **65:**1049–1063.
72. **Mermod M, Magnani D, Solioz M, Stoyanov JV.** 2012. The copper-inducible ComR (YcfQ) repressor regulates expression of ComC (YcfR), which affects copper permeability of the outer membrane of *Escherichia coli*. Biometals. **25:**33–43.
73. **Reichheld SE, Yu Z, Davidson AR.** 2009. The induction of folding cooperativity by ligand binding drives the allosteric response of tetracycline repressor. Proc. Natl. Acad. Sci. U. S. A. **106:**22263–22268.
74. **Sevvana M, Goetz C, Goeke D, Wimmer C, Berens C, Hillen W, Muller YA.** 2012. An exclusive α/β code directs allostery in TetR-peptide complexes. J. Mol. Biol. **416:**46–56.
75. **Abbas A, Morrissey P, Marquez C, Sheehan M, Delany R, O'Gara F.** 2002. Characterization of interactions between the transcriptional repressor PhlF and its binding Site at the *phlA* promoter in *Pseudomonas fluorescens* F113. J. Bacteriol. **184:**3008–3016.
76. **Le TB, Schumacher MA, Lawson DM, Brennan RG, Buttner MJ.** 2011. The crystal structure of the TetR family transcriptional repressor SimR bound to DNA and the role of a flexible N-terminal extension in minor groove binding. Nucleic Acids Res. **39:**9433–9447.
77. **Namwat W, Lee CK, Kinoshita H, Yamada Y, Nihira T.** 2001. Identification of the *varR* gene as a transcriptional regulator of virginiamycin S resistance in *Streptomyces virginiae*. J. Bacteriol. **183:**2025–2031.
78. **Ostash I, Ostash B, Luzhetskyy A, Bechthold A, Walker S, Fedorenko V.** 2008. Coordination of export and glycosylation of landomycins in *Streptomyces cyanogenus* S136. FEMS Microbiol. Lett. **285:**195–202.
79. **Tahlan K, Ahn SK, Sing A, Bodnaruk TD, Willems AR, Davidson AR, Nodwell JR.** 2007. Initiation of actinorhodin export in *Streptomyces coelicolor*. Mol. Microbiol. **63:**951–961.
80. **Das A, Khosla C.** 2009. Biosynthesis of aromatic polyketides in bacteria. Acc. Chem. Res. **42:**631–639.
81. **Xu Y, Willems A, Au-Yeung C, Tahlan K, Nodwell JR.** 2012. A two-step mechanism for the activation of actinorhodin export and resistance in *Streptomyces coelicolor*. mBio **3**(5)**:**e00191–12. doi:10.1128/mBio.00191-12.
82. **Bystrykh LV, Fernández-Moreno MA, Herrema JK, Malpartida F, Hopwood DA, Dijkhuizen L.** 1996. Production of actinorhodin-related "blue pigments" by *Streptomyces coelicolor* A3(2). J. Bacteriol. **178:**2238–2244.
83. **Erb A, Luzhetskyy A, Hardter U, Bechthold A.** 2009. Cloning and sequencing of the biosynthetic gene cluster for saquayamycin Z and galtamycin B and the elucidation of the assembly of their saccharide chains. Chembiochem **10:**1392–1401.
84. **Faust B, Hoffmeister D, Weitnauer G, Westrich L, Haag S, Schneider P, Decker H, Künzel E, Rohr J, Bechthold A.** 2000. Two new tailoring enzymes, a glycosyltransferase and an oxygenase, involved in biosynthesis of the angucycline antibiotic urdamycin A in *Streptomyces fradiae* Tü2717. Microbiology **146:**147–154.
85. **Galm U, Schimana J, Fiedler HP, Schmidt J, Li SM, Heide L.** 2002. Cloning and analysis of the simocyclinone biosynthetic gene cluster of *Streptomyces antibioticus* Tü 6040. Arch. Microbiol. **178:**102–114.
86. **Trefzer A, Pelzer S, Schimana J, Stockert S, Bihlmaier C, Fiedler HP, Welzel K, Vente A, Bechthold A.** 2002. Biosynthetic gene cluster of simocyclinone, a natural multihybrid antibiotic. Antimicrob. Agents. Chemother. **46:**1174–1182.
87. **Edwards MJ, Flatman RH, Mitchenall LA, Stevenson CE, Le TB, Clarke TA, McKay AR, Fiedler HP, Buttner MJ, Lawson DM, Maxwell**

A. 2009. A crystal structure of the bifunctional antibiotic simocyclinone D8, bound to DNA gyrase. Science **326:**1415–1418.
88. **Flatman RH, Howells AJ, Heide L, Fiedler HP, Maxwell A.** 2005. Simocyclinone D8, an inhibitor of DNA gyrase with a novel mode of action. Antimicrob. Agents Chemother. **49:**1093–1100.
89. **Bangera MG, Thomashow LS.** 1999. Identification and characterization of a gene cluster for synthesis of the polyketide antibiotic 2,4-diacetylphloroglucinol from *Pseudomonas fluorescens* Q2-87. J. Bacteriol. **181:**3155–3163.
90. **Gross H, Loper JE.** 2009. Genomics of secondary metabolite production by *Pseudomonas* spp. Nat. Prod. Rep. **26:**1408–1446.
91. **August PR, Tang L, Yoon YJ, Ning S, Müller R, Yu TW, Taylor M, Hoffmann D, Kim CG, Zhang X, Hutchinson CR, Floss HG.** 1998. Biosynthesis of the ansamycin antibiotic rifamycin: deductions from the molecular analysis of the *rif* biosynthetic gene cluster of *Amycolatopsis mediterranei* S699. Chem. Biol. **5:**69–79.
92. **Jørgensen H, Degnes Dikiy KF, Fjaervik A, Klinkenberg E, Gand Zotchev SB.** 2010. Insights into the evolution of macrolactam biosynthesis through cloning and comparative analysis of the biosynthetic gene cluster for a novel macrocyclic lactam, ML-449. Appl. Environ. Microbiol. **76:**283–293.
93. **Wu Q, Liang J, Lin S, Zhou X, Bai L, Deng Z, Wang Z.** 2011. Characterization of the biosynthesis gene cluster for the pyrrole polyether antibiotic calcimycin (A23187) in *Streptomyces chartreusis* NRRL 3882. Antimicrob. Agents. Chemother. **55:**974–982.
94. **Keller U, Lang M, Crnovcic I, Pfennig F, Schauwecker F.** 2010. The actinomycin biosynthetic gene cluster of *Streptomyces chrysomallus*: a genetic hall of mirrors for synthesis of a molecule with mirror symmetry. J. Bacteriol. **192:**2583–2595.
95. **Zhang G, Zhang H, Li S, Xiao J, Zhang G, Zhu Y, Niu S, Ju J, Zhang C.** 2012. Characterization of the amicetin biosynthesis gene cluster from *Streptomyces vinaceusdrappus* NRRL 2363 implicates two alternative strategies for amide bond formation. Appl. Environ. Microbiol. **78:**2393–2401.
96. **D'Costa VM, McGrann KM, Hughes DW, Wright GD.** 2006. Sampling the antibiotic resistome. Science **311:**374–377.
97. **Benveniste R, Davies J.** 1973. Aminoglycoside antibiotic-inactivating enzymes in actinomycetes similar to those present in clinical isolates of antibiotic-resistant bacteria. Proc. Natl. Acad. Sci. U. S. A. **70:**2276–2280.
98. **Wright GD.** 2010. Antibiotic resistance in the environment: a link to the clinic? Curr. Opin. Microbiol. **13:**589–594.
99. **Pickens LB, Kim W, Wang P, Zhou H, Watanabe K, Gomi S, Tang Y.** 2009. Biochemical analysis of the biosynthetic pathway of an anticancer tetracycline SF2575. J. Am. Chem. Soc. **131:**17677–17689.
100. **Folcher M, Morris RP, Dale G, Salah-Bey-Hocini K, Viollier PH, Thompson CJ.** 2001. A transcriptional regulator of a pristinamycin resistance gene in *Streptomyces coelicolor*. J. Biol. Chem. **276:**1479–1485.
101. **Noguchi N, Takada K, Katayama J, Emura A, Sasatsu M.** 2000. Regulation of transcription of the *mph*(*A*) gene for macrolide 2′-phosphotransferase I in *Escherichia coli*: characterization of the regulatory gene *mphR*(*A*). J. Bacteriol. **182:**5052–5058.
102. **Szczepanowski R, Krahn I, Bohn N, A Pühler, Schlüter A.** 2007. Novel macrolide resistance module carried by the IncP-1beta resistance plasmid pRSB111, isolated from a wastewater treatment plant. Antimicrob. Agents Chemother. **51:**673–678.
103. **Achard A, Guérin-Faublée V, Pichereau V, Villers C, Leclercq R.** 2008. Emergence of macrolide resistance gene *mph*(*B*) in *Streptococcus uberis* and cooperative effects with *rdmC*-like gene. Antimicrob. Agents Chemother. **52:**2767–2770.
104. **Hirooka K, Kunikane S, Matsuoka H, Yoshida K, Kumamoto K, Tojo S, Fujita Y.** 2007. Dual regulation of the *Bacillus subtilis* regulon comprising the *lmrAB* and *yxaGH* operons and *yxaF* gene by two transcriptional repressors, LmrA and YxaF, in response to flavonoids. J. Bacteriol. **189:**5170–5182.
105. **Baulard AR, Betts JC, Engohang-Ndong J, Quan S, McAdam RA, Brennan PJ, Locht C, Besra GS.** 2000. Activation of the pro-drug ethionamide is regulated in mycobacteria. J. Biol. Chem. **275:**28326–28331.
106. **DeBarber AE, Mdluli K, Bosman M, Bekker LG, Barry CE.** 2000. Ethionamide activation and sensitivity in multidrug-resistant *Mycobacterium tuberculosis*. Proc. Natl. Acad. Sci. U. S. A. **97:**9677–9682.
107. **Fraaije MW, Kamerbeek NM, Heidekamp AJ, Fortin R, Janssen DB.** 2004. The prodrug activator EtaA from *Mycobacterium tuberculosis* is a Baeyer-Villiger monooxygenase. J. Biol. Chem. **279:**3354–3360.
108. **Vannelli TA, Dykman A, Ortiz de Montellano PR.** 2002. The antituberculosis drug ethionamide is activated by a flavoprotein monooxygenase. J. Biol. Chem. **277:**12824–12829.
109. **Dover LG, Alahari A, Gratraud P, Gomes JM, Bhowruth V, Reynolds RC, Besra GS, Kremer L.** 2007. EthA, a common activator of thiocarbamide-containing drugs acting on different mycobacterial targets. Antimicrob. Agents Chemother. **51:**1055–1063.
110. **Qian L, Ortiz de Montellano PR.** 2006. Oxidative activation of thiacetazone by the *Mycobacterium tuberculosis* flavin monooxygenase EtaA and human FMO1 and FMO3. Chem. Res. Toxicol. **19:**443–449.
111. **Aires JR, Köhler T, Nikaido H, Plésiat P.** 1999. Involvement of an active efflux system in the natural resistance of *Pseudomonas aeruginosa* to aminoglycosides. Antimicrob. Agents Chemother. **43:**2624–2628.
112. **Ma D, Alberti M, Lynch C, Nikaido H, Hearst JE.** 1996. The local repressor AcrR plays a modulating role in the regulation of *acrA*B genes of *Escherichia coli* by global stress signals. Mol. Microbiol. **19:**101–112.
113. **Rahmati S, Yang S, Davidson AL, Zechiedrich EL.** 2002. Control of the AcrAB multidrug efflux pump by quorum-sensing regulator SdiA. Mol. Microbiol. **43:**677–685.
114. **White DG, Goldman JD, Demple B, Levy SB.** 1997. Role of the *acrAB* locus in organic solvent tolerance mediated by expression of *marA*, *soxS*, or *robA* in *Escherichia coli*. J. Bacteriol. **179:**6122–6126.
115. **Gibson JS, Cobbold RN, Kyaw-Tanner MT, Heisig P, Trott DJ.** 2010. Fluoroquinolone resistance mechanisms in multidrug-resistant *Escherichia coli* isolated from extraintestinal infections in dogs. Vet. Microbiol. **146:**161–166.
116. **Su CC, Rutherford DJ, Yu EW.** 2007. Characterization of the multidrug efflux regulator AcrR from *Escherichia coli*. Biochem. Biophys. Res. Commun. **361:**85–90.
117. **Li XZ, Nikaido H.** 2009. Efflux-mediated drug resistance in bacteria: an update. Drugs **69:**1555–1623.
118. **Vogne C, Aires JR, Bailly C, Hocquet D, Plésiat P.** 2004. Role of the multidrug efflux system MexXY in the emergence of moderate resistance to aminoglycosides among *Pseudomonas aeruginosa* isolates from patients with cystic fibrosis. Antimicrob. Agents Chemother. **48:**1676–1680.
119. **Poole K.** 2007. Efflux pumps as antimicrobial resistance mechanisms. Ann. Med. **39:**162–176.
120. **Helling B, Janes K, Kimball H, Tran T, Bundesmann M, Check P, Phelan D, Miller C.** 2002. Toxic waste disposal in *Escherichia coli*. J. Bacteriol. **184:**3699–3703.
121. **Caughlan RE, Sriram S, Daigle DM, Woods AL, Buco J, Peterson RL, Dzink-Fox J, Walker S, Dean CR.** 2009. Fmt bypass in *Pseudomonas aeruginosa* causes induction of MexXY efflux pump expression. Antimicrob. Agents Chemother. **53:**5015–5021.
122. **Morita Y, Tomida J, Kawamura Y.** 2012. Primary mechanisms mediating aminoglycoside resistance in the multidrug-resistant *Pseudomonas aeruginosa* clinical isolate PA7. Microbiology **158:**1071–1083.
123. **Hay T, Fraud S, Lau CH, Gilmour C, Poole K.** 2013. Antibiotic inducibility of the *mexXY* multidrug efflux operon of *Pseudomonas aeruginosa*: involvement of the MexZ anti-repressor ArmZ. PLoS One **8:**e56858. doi:10.1371/journal.pone.0056858.
124. **Tanaka N, Shuman S.** 2011. RtcB is the RNA ligase component of an *Escherichia coli* RNA repair operon. J. Biol. Chem. **286:**7727–7731.
125. **Baranov PV, Vestergaard B, Hamelryck T, Gesteland RF, Nyborg J, Atkins JF.** 2006. Diverse bacterial genomes encode an operon of two genes, one of which is an unusual class-I release factor that potentially recognizes atypical mRNA signals other than normal stop codons. Biol. Direct **1:**28.
126. **Khokhlov AS, Tovarova II, Borisova LN, Pliner SA, Shevchenko LN, Kornitskaia EI, Ivkina NS, Rapoport IA.** 1967. The A-factor, responsible for streptomycin biosynthesis by mutant strains of *Actinomyces streptomycini*. Dokl. Akad. Nauk. SSSR **177:**232–235.
127. **Kitani S, Hoshika M, Nihira T.** 2008. Disruption of *sscR* encoding a gamma-butyrolactone autoregulator receptor in *Streptomyces scabies* NBRC 12914 affects production of secondary metabolites. Folia Microbiol. (Praha) **53:**115–124.
128. **Corre C, Song L, O'Rourke S, Chater KF, Challis GL.** 2008. 2-Alkyl-4-hydroxymethylfuran-3-carboxylic acids, antibiotic production inducers discovered by *Streptomyces coelicolor* genome mining. Proc. Natl. Acad. Sci. U. S. A. **105:**17510–17515.

129. **D'Alia D, Eggle D, Nieselt K, Hu WS, Breitling R, Takano E.** 2011. Deletion of the signalling molecule synthase ScbA has pleiotropic effects on secondary metabolite biosynthesis, morphological differentiation and primary metabolism in *Streptomyces coelicolor* A3(2). Microb. Biotechnol. **4:**239–251.
130. **Takano E.** 2006. Gamma-butyrolactones: *Streptomyces* signalling molecules regulating antibiotic production and differentiation. Curr. Opin. Microbiol. **9:**287–294.
131. **Gottelt M, Kol S, Gomez-Escribano JP, Bibb M, Takano E.** 2010. Deletion of a regulatory gene within the *cpk* gene cluster reveals novel antibacterial activity in *Streptomyces coelicolor* A3(2). Microbiology **156:** 2343–2353.
132. **Wang J, Wang W, Wang L, Zhang G, Fan K, Tan H, Yang K.** 2011. A novel role of 'pseudo'γ-butyrolactone receptors in controlling γ-butyrolactone biosynthesis in *Streptomyces*. Mol. Microbiol. **82:** 236–250.
133. **Xu G, Wang J, Wang L, Tian X, Yang H, Fan K, Yang K, Tan H.** 2010. "Pseudo" gamma-butyrolactone receptors respond to antibiotic signals to coordinate antibiotic biosynthesis. J. Biol. Chem. **285:**27440–27448.
134. **Onaka H, Nakagawa T, Horinouchi S.** 1998. Involvement of two A-factor receptor homologues in *Streptomyces coelicolor* A3(2) in the regulation of secondary metabolism and morphogenesis. Mol. Microbiol. **28:** 743–753.
135. **Boyer M, Wisniewski-Dyé F.** 2009. Cell-cell signalling in bacteria: not simply a matter of quorum. FEMS Microbiol. Ecol. **70:**1–19.
136. **Michael B, Smith JN, Swift S, Heffron F, Ahmer BM.** 2001. SdiA of *Salmonella enterica* is a LuxR homolog that detects mixed microbial communities. J. Bacteriol. **183:**5733–5742.
137. **Rutherford ST, van Kessel JC, Shao Y, Bassler BL.** 2011. AphA and LuxR/HapR reciprocally control quorum sensing in vibrios. Genes Dev. **25:**397–408.
138. **Kim Y, Kim BS, Park YJ, Choi WC, Hwang J, Kang BS, Oh TK, Choi SH, Kim MH.** 2010. Crystal structure of SmcR, a quorum-sensing master regulator of *Vibrio vulnificus*, provides insight into its regulation of transcription. J. Biol. Chem. **285:**14020–14030.
139. **De Silva RS, Kovacikova G, Lin W, Taylor RK, Skorupski K, Kull FJ.** 2007. Crystal structure of the *Vibrio cholerae* quorum-sensing regulatory protein HapR. J. Bacteriol. **189:**5683–5691.
140. **Lenz DH, Mok KC, Lilley BN, Kulkarni RV, Wingreen NS, Bassler BL.** 2004. The small RNA chaperone Hfq and multiple small RNAs control quorum sensing in *Vibrio harveyi* and *Vibrio cholerae*. Cell **118:**69–82.
141. **Tsou AM, Liu Z, Cai T, Zhu J.** 2011. The VarS/VarA two-component system modulates the activity of the *Vibrio cholerae* quorum-sensing transcriptional regulator HapR. Microbiology **157:**1620–1628.
142. **Zhang L, Li W, He ZG.** 2013. DarR, a TetR-like transcriptional factor, is a cyclic-di-AMP responsive repressor in *Mycobacterium smegmatis*. J. Biol. Chem. **288:**3085–3096.
143. **Poelarends J, Kulakov A, Larkin J, JET van Hylckama Vlieg Janssen B.** 2000. Roles of horizontal gene transfer and gene integration in evolution of 1,3-dichloropropene- and 1,2-dibromoethane-degradative pathways. J. Bacteriol. **182:**2191–2199.
144. **Providenti MA, Shaye RE, Lynes KD, McKenna NT, JM O'brien, Rosolen S, Wyndham RC, Lambert IB.** 2006. The locus coding for the 3-nitrobenzoate dioxygenase of *Comamonas* sp. strain JS46 is flanked by IS1071 elements and is subject to deletion and inversion events. Appl. Environ. Microbiol. **72:**2651–2660.
145. **Krug A, Wendisch VF, Bott M.** 2005. Identification of AcnR, a TetR-type repressor of the aconitase gene *acn* in *Corynebacterium glutamicum*. J. Biol. Chem. **280:**585–595.
146. **Garcia-Nafria J, Baumgart M, Turkenburg JP, Wilkinson AJ, Bott M, Wilson KS.** 2013. Crystal and solution studies reveal that the transcriptional regulator AcnR of *Corynebacterium glutamicum* is regulated by citrate:Mg^{2+} binding to a non-canonical pocket. J. Biol. Chem. **288:** 15800–15812.
147. **Park H, Ro YT, Kim YM.** 2011. MdoR is a novel positive transcriptional regulator for the oxidation of methanol in *Mycobacterium* sp. strain JC1. J. Bacteriol. **193:**6288–6294.
148. **Jiménez JI, Juárez JF, García JL, Díaz E.** 2011. A finely tuned regulatory circuit of the nicotinic acid degradation pathway in *Pseudomonas putida*. Environ. Microbiol. **13:**1718–1732.
149. **Li T, Zhao K, Huang Y, Li D, Jiang CY, Zhou N, Fan Z, Liu SJ.** 2012. The TetR-type transcriptional repressor RolR from *Corynebacterium glutamicum* regulates resorcinol catabolism by binding to a unique operator, *rolO*. Appl. Environ. Microbiol. **78:**6009–6016.
150. **Sakamoto K, Agari Y, Kuramitsu S, Shinkai A.** 2011. Phenylacetyl coenzyme A is an effector molecule of the TetR family transcriptional repressor PaaR from *Thermus thermophilus* HB8. Bacteriol. **193:**4388–4395.
151. **Amon J, Titgemeyer F, Burkovski A.** 2009. A genomic view on nitrogen metabolism and nitrogen control in mycobacteria. J. Mol. Microbiol. Biotechnol. **17:**20–29.
152. **Fink D, Weissschuh N, Reuther J, Wohlleben W, Engels A.** 2002. Two transcriptional regulators GlnR and GlnRII are involved in regulation of nitrogen metabolism in *Streptomyces coelicolor* A3(2). Mol. Microbiol. **46:**331–347.
153. **Shimada T, Hirao K, Kori A, Yamamoto K, Ishihama A.** 2007. RutR is the uracil/thymine-sensing master regulator of a set of genes for synthesis and degradation of pyrimidines. Mol. Microbiol. **66:**744–757.
154. **Hidese R, Mihara H, Kurihara T, Esaki N.** 2012. *Pseudomonas putida* PydR, a RutR-like transcriptional regulator, represses the dihydropyrimidine dehydrogenase gene in the pyrimidine reductive catabolic pathway. J. Biochem. **152:**341–346.
155. **Nguyen Ple M, Bervoets I, Maes D, Charlier D.** 2010. The protein-DNA contacts in RutR · carAB operator complexes. Nucleic Acids Res. **38:**6286–6300.
156. **Hillerich B, Westpheling J.** 2008. A new TetR family transcriptional regulator required for morphogenesis in *Streptomyces coelicolor*. J. Bacteriol. **190:**61–67.
157. **Nickel J, Irzik K, van Ooyen J, Eggeling L.** 2010. The TetR-type transcriptional regulator FasR of *Corynebacterium glutamicum* controls genes of lipid synthesis during growth on acetate. Mol. Microbiol. **78:** 253–265.
158. **Chen CH, Cheng JC, Cho YC, Hsu WH.** 2005. A gene cluster for the fatty acid catabolism from *Pseudonocardia autotrophica* BCRC12444. Biochem. Biophys. Res. Commun. **329:**863–868.
159. **Chen L, Chen J, Jiang Y, Zhang W, Jiang W, Lu Y.** 2009. Transcriptomics analyses reveal global roles of the regulator AveI in *Streptomyces avermitilis*. FEMS Microbiol. Lett. **298:**199–207.
160. **Lee HN, Huang J, Im JH, Kim SH, Noh JH, Cohen SN, Kim ES.** 2010. Putative TetR family transcriptional regulator SCO1712 encodes an antibiotic downregulator in *Streptomyces coelicolor*. Appl. Environ. Microbiol. **76:**3039–3043.
161. **Matsuoka H, Hirooka K, Fujita Y.** 2007. Organization and function of the YsiA regulon of *Bacillus subtilis* involved in fatty acid degradation. J. Biol. Chem. **282:**5180–5194.
162. **Anand S, Singh V, Singh AK, Mittal M, Datt M, Subramani B, Kumaran S.** 2012. Equilibrium binding and kinetic characterization of putative tetracycline repressor family transcription regulator Fad35R from *Mycobacterium tuberculosis*. FEBS. J. **279:**3214–3228.
163. **Kang Y, Nguyen DT, Son MS, Hoang TT.** 2008. The *Pseudomonas aeruginosa* PsrA responds to long-chain fatty acid signals to regulate the *fadBA5* beta-oxidation operon. Microbiology **154:**1584–1598.
164. **Zhang YM, Marrakchi H, Rock CO.** 2002. The FabR (YijC) transcription factor regulates unsaturated fatty acid biosynthesis in *Escherichia coli*. J. Biol. Chem. **277:**15558–15565.
165. **Feng Y, Cronan JE.** 2011. Complex binding of the FabR repressor of bacterial unsaturated fatty acid biosynthesis to its cognate promoters. Mol. Microbiol. **80:**195–218.
166. **Zhang YM, Zhu K, Frank MW, Rock CO.** 2007. A *Pseudomonas aeruginosa* transcription factor that senses fatty acid structure. Mol. Microbiol. **66:**622–632.
167. **de Eugenio LI, Galán B, Escapa IF, Maestro B, Sanz JM, García JL, Prieto MA.** 2010. The PhaD regulator controls the simultaneous expression of the *pha* genes involved in polyhydroxyalkanoate metabolism and turnover in *Pseudomonas putida* KT2442. Environ. Microbiol. **12:**1591–1603.
168. **Rehm BH.** 2010. Bacterial polymers: biosynthesis, modifications and applications. Nat. Rev. Microbiol. **8:**578–592.
169. **Kendall SL, Burgess P, Balhana R, Withers M, Ten Bokum A, Lott JS, Gao C, Uhia-Castro I, Stoker NG.** 2010. Cholesterol utilization in mycobacteria is controlled by two TetR-type transcriptional regulators: *kstR* and *kstR2*. Microbiology **156:**1362–1371.
170. **Kendall SL, Withers M, Soffair CN, Moreland NJ, Gurcha S, Sidders B, Frita R, Ten Bokum A, Besra GS, Lott JS, Stoker NG.** 2007. A highly conserved transcriptional repressor controls a large regulon involved in

lipid degradation in *Mycobacterium smegmatis* and *Mycobacterium tuberculosis*. Mol. Microbiol. **65:**684–699.
171. **Uhía I, Galán B, Kendall SL, Stoker NG, García JL.** 2012. Cholesterol metabolism in *Mycobacterium smegmatis*. Environ. Microbiol. Rep. **4:**168–182.
172. **Van der Geize R, Yam K, Heuser T, Wilbrink MH, Hara H, Anderton MC, Sim E, Dijkhuizen L, Davies JE, Mohn WW, Eltis LD.** 2007. A gene cluster encoding cholesterol catabolism in a soil actinomycete provides insight into *Mycobacterium tuberculosis* survival in macrophages. Proc. Natl. Acad. Sci. U. S. A. **104:**1947–1952.
173. **Rengarajan J, Bloom BR, Rubin EJ.** 2005. Genome-wide requirements for *Mycobacterium tuberculosis* adaptation and survival in macrophages. Proc. Natl. Acad. Sci. U. S. A. **102:**8327–8332.
174. **Förster-Fromme K, Jendrossek D.** 2010. AtuR is a repressor of acyclic terpene utilization (*atu*) gene cluster expression and specifically binds to two 13 bp inverted repeat sequences of the *atuA-atuR* intergenic region. FEMS Microbiol. Lett. **308:**166–174.
175. **Eaton RW.** 1996. *p*-Cumate catabolic pathway in *Pseudomonas putida* Fl: cloning and characterization of DNA carrying the *cmt* operon. J. Bacteriol. **178:**1351–1362.
176. **Eaton RW.** 1997. *p*-Cymene catabolic pathway in *Pseudomonas putida* F1: cloning and characterization of DNA encoding conversion of *p*-cymene to *p*-cumate. J. Bacteriol. **179:**3171–3180.
177. **Grogan G, Roberts GA, Bougioukou D, Turner NJ, Flitsch SL.** 2001. The desymmetrization of bicyclic beta-diketones by an enzymatic retro-Claisen reaction. A new reaction of the crotonase superfamily. J. Biol. Chem. **276:**12565–12572.
178. **Lee K, Ryu EK, Choi KS, Cho MC, Jeong JJ, Choi EN, Lee SO, Yoon DY, Hwang I, Kim CK.** 2006. Identification and expression of the *cym*, cmt, and *tod* catabolic genes from *Pseudomonas putida* KL47: expression of the regulatory *todST* genes as a factor for catabolic adaptation. J. Microbiol. **44:**192–199.
179. **Puskás LG, Inui M, Kele Z, Yukawa H.** 2000. Cloning of genes participating in aerobic biodegradation of *p*-cumate from *Rhodopseudomonas palustris*. DNA Seq. **11:**9–20.
180. **Satriano J.** 2003. Agmatine: at the crossroads of the arginine pathways. Ann. N. Y. Acad. Sci. **1009:**34–43.
181. **Nakada Y, Jiang Y, Nishijyo T, Itoh Y, Lu CD.** 2001. Molecular characterization and regulation of the *aguBA* operon, responsible for agmatine utilization in *Pseudomonas aeruginosa*. PAO1. J. Bacteriol. **183:**6517–6524.
182. **Williams BJ, Du RH, Calcutt MW, Abdolrasulnia R, Christman BW, Blackwell TS.** 2010. Discovery of an operon that participates in agmatine metabolism and regulates biofilm formation in *Pseudomonas aeruginosa*. Mol. Microbiol. **76:**104–119.
183. **Kazakov AE, Rodionov DA, Alm E, Arkin AP, Dubchak I, Gelfand MS.** 2009. Comparative genomics of regulation of fatty acid and branched-chain amino acid utilization in proteobacteria. J. Bacteriol. **191:**52–64.
184. **Rey DA, Pühler A, Kalinowski J.** 2003. The putative transcriptional repressor McbR, member of the TetR-family, is involved in the regulation of the metabolic network directing the synthesis of sulfur containing amino acids in *Corynebacterium glutamicum*. J. Biotechnol. **103:**51–65.
185. **Rey DA, Nentwich SS, Koch DJ, Rückert C, Pühler A, Tauch A, Kalinowski J.** 2005. The McbR repressor modulated by the effector substance S-adenosylhomocysteine controls directly the transcription of a regulon involved in sulphur metabolism of *Corynebacterium glutamicum* ATCC 13032. Mol. Microbiol. **56:**871–887.
186. **Krömer JO, Bolten CJ, Heinzle E, Schröder H, Wittmann C.** 2008. Physiological response of *Corynebacterium glutamicum* to oxidative stress induced by deletion of the transcriptional repressor McbR. Microbiology **154:**3917–3930.
187. **Howard PK, Shaw J, Otsuka AJ.** 1985. Nucleotide sequence of the *birA* gene encoding the biotin operon repressor and biotin holoenzyme synthetase functions of *Escherichia coli*. Gene **35:**321–331.
188. **Rodionov DA, Gelfand MS.** 2006. Computational identification of BioR, a transcriptional regulator of biotin metabolism in Alphaproteobacteria, and of its binding signal. FEMS Microbiol. Lett. **255:**102–107.
189. **Brune I, Götker S, Schneider J, Rodionov DA, Tauch A.** 2012. Negative transcriptional control of biotin metabolism genes by the TetR-type regulator BioQ in biotin-auxotrophic *Corynebacterium glutamicum* ATCC 13032. J. Biotechnol. **159:**225–234.
190. **Hashimoto Y, Yamashita M, Murooka Y.** 1997. The *Propionibacterium freudenreichii hemYHBXRL* gene cluster, which encodes enzymes and a regulator involved in the biosynthetic pathway from glutamate to protoheme. Appl. Microbiol. Biotechnol. **47:**385–392.
191. **Lechardeur D, Cesselin B, Liebl U, Vos MH, Fernandez A, Brun C, Gruss A, Gaudu P.** 2012. Discovery of intracellular heme-binding protein HrtR, which controls heme efflux by the conserved HrtB-HrtA transporter in *Lactococcus lactis*. J. Biol. Chem. **287:**4752–4758.
192. **Cho H, McManus HR, Dove SL, Bernhardt TG.** 2011. Nucleoid occlusion factor SlmA is a DNA-activated FtsZ polymerization antagonist. Proc. Natl. Acad. Sci. U. S. A. **108:**3773–3778.
193. **Tonthat NK, Arold ST, Pickering BF, Van Dyke MW, Liang S, Lu Y, Beuria TK, Margolin W, Schumacher MA.** 2011. Molecular mechanism by which the nucleoid occlusion factor, SlmA, keeps cytokinesis in check. EMBO. J. **30:**154–164.
194. **Wu LJ, Errington J.** 2012. Nucleoid occlusion and bacterial cell division. Nat. Rev. Microbiol. **10:**8–12.
195. **Wagner-Herman JK, Bernard R, Dunne R, Bisson-Filho AW, Kumar K, Nyguen T, Mulcahy L, Koullias J, Gueiros-Filho FJ, Rudner DZ.** 2012. RefZ facilitates the switch from medial to polar division during spore formation in Bacillus subtilis. J. Bacteriol. **194:**4608–4618.
196. **Martin RG, Rosner JL.** 2001. The AraC transcriptional activators. Curr. Opin. Microbiol. **4:**132–137.
197. **Cherney LT, Cherney MM, Garen CR, Lu GJ, James MN.** 2008. Crystal structure of the arginine repressor protein in complex with the DNA operator from *Mycobacterium tuberculosis*. J. Mol. Biol. **384:**1330–1340.
198. **Busenlehner LS, Pennella MA, Giedroc DP.** 2003. The SmtB/ArsR family of metalloregulatory transcriptional repressors: Structural insights into prokaryotic metal resistance. FEMS Microbiol. Rev. **27:**131–143.
199. **Yokoyama K, Ishijima SA, Clowney L, Koike H, Aramaki H, Tanaka C, Makino K, Suzuki M.** 2006. Feast/famine regulatory proteins (FFRPs): *Escherichia coli* Lrp, AsnC and related archaeal transcription factors. FEMS Microbiol. Rev. **30:**89–108.
200. **Körner H, Sofia HJ, Zumft WG.** 2003. Phylogeny of the bacterial superfamily of Crp-Fnr transcription regulators: exploiting the metabolic spectrum by controlling alternative gene programs. FEMS Microbiol. Rev. **27:**559–592.
201. **Zeng G, Ye S, Larson TJ.** 1996. Repressor for the sn-glycerol 3-phosphate regulon of *Escherichia coli* K-12: primary structure and identification of the DNA-binding domain. J. Bacteriol. **178:**7080–7089.
202. **Pennella MA, Giedroc DP.** 2005. Structural determinants of metal selectivity in prokaryotic metal-responsive transcriptional regulators. Biometals **18:**413–428.
203. **Rigali S, Derouaux A, Giannotta F, Dusart J.** 2002. Subdivision of the helix-turn-helix GntR family of bacterial regulators in the FadR, HutC, MocR, and YtrA subfamilies. J. Biol. Chem. **277:**12507–12515.
204. **Molina-Henares AJ, Krell T, Eugenia Guazzaroni M, Segura A, Ramos JL.** 2006. Members of the IclR family of bacterial transcriptional regulators function as activators and/or repressors. FEMS Microbiol. Rev. **30:**157–186.
205. **Swint-Kruse L, Matthews KS.** 2009. Allostery in the LacI/GalR family: variations on a theme. Curr. Opin. Microbiol. **12:**129–137.
206. **Chen J, Xie J.** 2011. Role and regulation of bacterial LuxR-like regulators. J. Cell Biochem. **112:**2694–2702.
207. **Maddocks SE, Oyston PC.** 2008. Structure and function of the LysR-type transcriptional regulator (LTTR) family proteins. Microbiology **154:**3609–3623.
208. **Wilkinson SP, Grove A.** 2006. Ligand-responsive transcriptional regulation by members of the MarR family of winged helix proteins. Curr. Issues Mol. Biol. **8:**51–62.
209. **Hobman JL, Wilkie J, Brown NL.** 2005. A design for life: prokaryotic metal-binding MerR family regulators. Biometals **18:**429–436.
210. **Self WT, Grunden AM, Hasona A, Shanmugam KT.** 1999. Transcriptional regulation of molybdoenzyme synthesis in *Escherichia coli* in response to molybdenum: ModE-molybdate, a repressor of the *modABCD* (molybdate transport) operon is a secondary transcriptional activator for the *hyc* and *nar* operons. Microbiology **145:**41–55.
211. **Huillet E, Velge P, Vallaeys T, Pardon P.** 2006. LadR, a new PadR-related transcriptional regulator from *Listeria monocytogenes*, negatively regulates the expression of the multidrug efflux pump MdrL. FEMS Microbiol. Lett. **254:**87–94.
212. **McDonnell GE, McConnell DJ.** 1994. Overproduction, isolation, and DNA-binding characteristics of Xre, the repressor protein from the *Bacillus subtilis* defective prophage PBSX. J. Bacteriol. **176:**5831–5834.

213. **Xu Q, van Wezel GP, Chiu HJ, Jaroszewski L, Klock HE, Knuth MW, Miller MD, Lesley SA, Godzik A, Elsliger MA, Deacon AM, Wilson IA.** 2012. Structure of an MmyB-like regulator from *C. aurantiacus*, member of a new transcription factor family linked to antibiotic metabolism in actinomycetes. PLoS One **7:**e41359. doi:10.1371/journal.pone.0041359.
214. **Gottardi EM, Krawczyk JM, von Suchodoletz H, Schadt S, Mühlenweg A, Uguru GC, Pelzer S, Fiedler HP, Bibb MJ, Stach JE, Süssmuth RD.** 2011. Abyssomicin biosynthesis: formation of an unusual polyketide, antibiotic-feeding studies and genetic analysis. Chembiochem **12:**1401–1410.
215. **Wang X, Tabudravu J, Rateb ME, Annand KJ, Qin Z, Jaspars M, Deng Z, Yu Y, Deng H.** 2013. Identification and characterization of the actinomycin G gene cluster in *Streptomyces iakyrus*. Mol. Biosyst. **9:**1286–1289.
216. **Johnson TJ, Jordan D, Kariyawasam S, Stell AL, Bell NP, Wannemuehler YM, Alarcón CF, Li G, Tivendale KA, Logue CM, Nolan LK.** 2010. Sequence analysis and characterization of a transferable hybrid plasmid encoding multidrug resistance and enabling zoonotic potential for extraintestinal *Escherichia coli*. Infect. Immun. **78:**1931–1942.
217. **Curson ARJ, Sullivan MJ, Todd JD, Johnston AWB.** 2011. DddY, a periplasmic dimethylsulfoniopropionate lyase found in taxonomically diverse species of Proteobacteria. ISME. J. **5:**1191–1200.
218. **Sullivan MJ, Curson AR, Shearer N, Todd JD, Green RT, Johnston AW.** 2011. Unusual regulation of a leaderless operon involved in the catabolism of dimethylsulfoniopropionate in *Rhodobacter sphaeroides*. PLoS One **6:**e15972. doi:10.1371/journal.pone.0015972.
219. **Rosenfeld N, Bouchier C, Courvalin P, Périchon B.** 2012. Expression of the resistance-nodulation-cell division pump AdeIJK in *Acinetobacter baumannii* is regulated by AdeN, a TetR-type regulator. Antimicrob. Agents Chemother. **56:**2504–2510.
220. **Oja T, Palmu K, Lehmussola H, Leppäranta O, K Hännikäinen, Niemi J, P Mäntsälä, Metsä-Ketelä M.** 2008. Characterization of the alnumycin gene cluster reveals unusual gene products for pyran ring formation and dioxan biosynthesis. Chem. Biol. **15:**1046–1057.
221. **Bunet R, Mendes MV, Rouhier N, Pang X, Hotel L, Leblond P, Aigle B.** 2008. Regulation of the synthesis of the angucyclinone antibiotic alpomycin in *Streptomyces ambofaciens* by the autoregulator receptor AlpZ and its specific ligand. J. Bacteriol. **190:**3293–3305.
222. **Bunet R, Song L, Mendes MV, Corre C, Hotel L, Rouhier N, Framboisier X, Leblond P, Challis GL, Aigle B.** 2011. Characterization and manipulation of the pathway-specific late regulator AlpW reveals *Streptomyces ambofaciens* as a new producer of kinamycins. J. Bacteriol. **193:**1142–1153.
223. **Peng WT, Nester EW.** 2001. Characterization of a putative RND-type efflux system in *Agrobacterium tumefaciens*. Gene **270:**245–252.
224. **Zhang H, Wang H, Wang Y, Cui H, Xie Z, Pu Y, Pei S, Li F, Qin S.** 2012. Genomic sequence-based discovery of novel angucyclinone antibiotics from marine *Streptomyces* sp. W007. FEMS Microbiol. Lett. **332:**105–112.
225. **Onaka H, Ando N, Nihira T, Yamada Y, Beppu T, Horinouchi S.** 1995. Cloning and characterization of the A-factor receptor gene from *Streptomyces griseus*. J. Bacteriol. **177:**6083–6092.
226. **Kieboom J, de Bont J.** 2001. Identification and molecular characterization of an efflux system involved in *Pseudomonas putida* S12 multidrug resistance. Microbiology **147:**43–51.
227. **Ng D, Chin HK, Wong VV.** 2009. Constitutive overexpression of *asm2* and *asm39* increases AP-3 production in the actinomycete *Actinosynnema pretiosum*. J. Ind. Microbiol. Biotechnol. **36:**1345–1351.
228. **Novakova R, Bistakova J, Homerova D, Rezuchova B, Kormanec J.** 2002. Cloning and characterization of a polyketide synthase gene cluster involved in biosynthesis of a proposed angucycline-like polyketide auricin in *Streptomyces aureofaciens* CCM 3239. Gene **297:**197–208.
229. **Novakova R, Kutas P, Feckova L, Kormanec J.** 2010. The role of the TetR-family transcriptional regulator Aur1R in negative regulation of the auricin gene cluster in *Streptomyces aureofaciens* CCM 3239. Microbiology **156:**2374–2383.
230. **Miyamoto KT, Kitani S, Komatsu M, Ikeda H, Nihira T.** 2011. The autoregulator receptor homologue AvaR3 plays a regulatory role in antibiotic production, mycelial aggregation and colony development of *Streptomyces avermitilis*. Microbiology **157:**2266–2275.
231. **Chen L, Lu Y, Chen J, Zhang W, Shu D, Qin Z, Yang S, Jiang W.** 2008. Characterization of a negative regulator AveI for avermectin biosynthesis in *Streptomyces avermitilis* NRRL8165. Appl. Microbiol. Biotechnol. **80:**277–286.
232. **Zhao Q, He Q, Ding W, Tang M, Kang Q, Yu Y, Deng W, Zhang Q, Fang J, Tang G, Liu W.** 2008. Characterization of the azinomycin B biosynthetic gene cluster revealing a different iterative type I polyketide synthase for naphthoate biosynthesis. Chem. Biol. **15:**693–705.
233. **Okamoto S, Nakamura K, Nihira T, Yamada Y.** 1995. Virginiae butanolide binding protein from *Streptomyces virginiae*. Evidence that VbrA is not the virginiae butanolide binding protein and reidentification of the true binding protein. J. Biol. Chem. **270:**12319–12326.
234. **Matsuno K, Yamada Y, Lee CK, Nihira T.** 2004. Identification by gene deletion analysis of *barB* as a negative regulator controlling an early process of virginiamycin biosynthesis in *Streptomyces virginiae*. Arch. Microbiol. **181:**52–59.
235. **Kawachi R, Akashi T, Kamitani Y, Sy A, Wangchaisoonthorn U, Nihira T, Yamada Y.** 2000. Identification of an AfsA homologue (BarX) from *Streptomyces virginiae* as a pleiotropic regulator controlling autoregulator biosynthesis, virginiamycin biosynthesis and virginiamycin M1 resistance. Mol. Microbiol. **36:**302–313.
236. **Jørgensen H, Degnes KF, Sletta H, Fjaervik E, Dikiy A, Herfindal L, Bruheim P, Klinkenberg G, Bredholt H, Nygård G, Døskeland SO, Ellingsen TE, Zotchev SB.** 2009. Biosynthesis of macrolactam BE-14106 involves two distinct PKS systems and amino acid processing enzymes for generation of the aminoacyl starter unit. Chem. Biol. **16:**1109–1121.
237. **Martin FA, Posadas DM, Carrica MC, Cravero SL, O'Callaghan D, Zorreguieta A.** 2009. Interplay between two RND systems mediating antimicrobial resistance in *Brucella suis*. J. Bacteriol. **191:**2530–2540.
238. **Rkenes TP, Lamark T, Strøm AR.** 1996. DNA-binding properties of the BetI repressor protein of *Escherichia coli*: the inducer choline stimulates BetI-DNA complex formation. J. Bacteriol. **178:**1663–1670.
239. **Chan YY, Tan TM, Ong YM, Chua KL.** 2004. BpeAB-OprB, a multidrug efflux pump in *Burkholderia pseudomallei*. Antimicrob. Agents Chemother. **48:**1128–1135.
240. **Santamarta I, Pérez-Redondo R, Lorenzana LM, Martín JF, Liras P.** 2005. Different proteins bind to the butyrolactone receptor protein ARE sequence located upstream of the regulatory *ccaR* gene of *Streptomyces clavuligerus*. Mol. Microbiol. **56:**824–835.
241. **Schwartz KT, Carleton JD, Quillin SJ, Rollins SD, Portnoy DA, Leber JH.** 2012. Hyper-induction of host beta interferon by a *Listeria monocytogenes* strain naturally over-expressing the multi-drug efflux pump MdrT. Infect. Immun. **80:**1537–1545.
242. **Sun GW, Chen Y, Liu Y, Tan GY, Ong C, Tan P, Gan YH.** 2010. Identification of a regulatory cascade controlling type III secretion system 3 gene expression in *Burkholderia pseudomallei*. Mol. Microbiol. **76:**677–689.
243. **Kudo F, Numakura M, Tamegai H, Yamamoto H, Eguchi T, Kakinuma K.** 2005. Extended sequence and functional analysis of the butirosin biosynthetic gene cluster in *Bacillus circulans* SANK 72073. J. Antibiot. (Tokyo) **58:**373–379.
244. **Ahlert J, Shepard E, Lomovskaya N, Zazopoulos E, Staffa A, Bachmann BO, Huang K, Fonstein L, Czisny A, Whitwam RE, Farnet CM, Thorson JS.** 2002. The calicheamicin gene cluster and its iterative type I enediyne PKS. Science **297:**1173–1176.
245. **Koga H, Aramaki H, Yamaguchi E, Takeuchi K, Horiuchi T, Gunsalus IC.** 1986. *camR*, a negative regulator locus of the cytochrome P-450cam hydroxylase operon. J. Bacteriol. **166:**1089–1095.
246. **Xi C, Schoeters E, Vanderleyden J, Michiels J.** 2000. Symbiosis-specific expression of Rhizobium etli casA encoding a secreted calmodulin-related protein. Proc. Natl. Acad. Sci. U. S. A. **97:**11114–11119.
247. **Itou H, Watanabe N, Yao M, Shirakihara Y, Tanaka I.** 2010. Crystal structures of the multidrug binding repressor *Corynebacterium glutamicum* CgmR in complex with inducers and with an operator. J. Mol. Biol. **403:**174–184.
248. **Jia XY, Tian ZH, Shao L, Qu XD, Zhao QF, Tang J, Tang GL, Liu W.** 2006. Genetic characterization of the chlorothricin gene cluster as a model for spirotetronate antibiotic biosynthesis. Chem. Biol. **13:**575–585.
249. **Kharel MK, Subba B, Basnet DB, Woo JS, Lee HC, Liou K, Sohng JK.** 2004. A gene cluster for biosynthesis of kanamycin from *Streptomyces kanamyceticus*: comparison with gentamicin biosynthetic gene cluster. Arch. Biochem. Biophys. **429:**204–214.
250. **MacEachran DP, Stanton BA, O'Toole GA.** 2008. Cif is negatively

regulated by the TetR family repressor CifR. Infect. Immun. **76:**3197–3206.
251. **Takano E, Kinoshita H, Mersinias V, Bucca G, Hotchkiss G, Nihira T, Smith CP, Bibb M, Wohlleben W, Chater K.** 2005. A bacterial hormone (the SCB1) directly controls the expression of a pathway-specific regulatory gene in the cryptic type I polyketide biosynthetic gene cluster of *Streptomyces coelicolor*. Mol. Microbiol. **56:**465–479.
252. **Todd JD, Curson AR, Nikolaidou-Katsaraidou N, Brearley CA, Watmough NJ, Chan Y, Page PC, Sun L, Johnston AW.** 2010. Molecular dissection of bacterial acrylate catabolism—unexpected links with dimethylsulfoniopropionate catabolism and dimethyl sulfide production. Environ. Microbiol. **12:**327–343.
253. **Lee LF, Huang YJ, Chen CW.** 2003. Repressed multidrug resistance genes in *Streptomyces lividans*. Arch. Microbiol. **180:**176–184.
254. **Lee LF, Chen YJ, Kirby R, Chen C, Chen CW.** 2007. A multidrug efflux system is involved in colony growth in *Streptomyces lividans*. Microbiology **153:**924–934.
255. **Watanabe K, Hotta K, Praseuth AP, Koketsu K, Migita A, Boddy CN, Wang CC, Oguri H, Oikawa H.** 2006. Total biosynthesis of antitumor nonribosomal peptides in *Escherichia coli*. Nat. Chem. Biol. **2:**423–428.
256. **Hearn EM, Dennis JJ, Gray MR, Foght JM.** 2003. Identification and characterization of the *emhABC* efflux system for polycyclic aromatic hydrocarbons in *Pseudomonas fluorescens* cLP6a. J. Bacteriol. **185:**6233–6240.
257. **Tian T, Wu XG, Duan HM, Zhang LQ.** 2010. The resistance-nodulation-division efflux pump EmhABC influences the production of 2,4-diacetylphloroglucinol in *Pseudomonas fluorescens* 2P24. Microbiology **156:**39–48.
258. **Piel J, Hertweck C, Shipley PR, Hunt DM, Newman MS, Moore BS.** 2000. Cloning, sequencing and analysis of the enterocin biosynthesis gene cluster from the marine isolate '*Streptomyces maritimus*': evidence for the derailment of an aromatic polyketide synthase. Chem. Biol. **7:**943–955.
259. **Hirakawa H, Takumi-Kobayashi A, Theisen U, Hirata T, Nishino K, Yamaguchi A.** 2008. AcrS/EnvR represses expression of the *acrAB* multidrug efflux genes in *Escherichia coli*. J. Bacteriol. **190:**6276–6279.
260. **Rodríguez-García A, Santamarta I, Pérez-Redondo R, Martín JF, Liras P.** 2006. Characterization of a two-gene operon *epeRA* involved in multidrug resistance in *Streptomyces clavuligerus*. Res. Microbiol. **157:**559–568.
261. **Rui Z, Ye M, Wang S, Fujikawa K, Akerele B, Aung M, Floss HG, Zhang W, Yu TW.** 2012. Insights into a divergent phenazine biosynthetic pathway governed by a plasmid-born esmeraldin gene cluster. Chem. Biol. **19:**1116–1125.
262. **Waki M, Nihira T, Yamada Y.** 1997. Cloning and characterization of the gene (*farA*) encoding the receptor for an extracellular regulatory factor (IM-2) from *Streptomyces* sp. strain FRI-5. J. Bacteriol. **179:**5131–5137.
263. **Wenzel M, Lang K, T Günther, Bhandari A, Weiss A, Lulchev P, Szentgyörgyi E, Kranzusch B, Göttfert M.** 2012. Characterization of the flavonoid-responsive regulator FrrA and its binding sites. J. Bacteriol. **194:**2363–2370.
264. **Jobling MG, Holmes RK.** 1997. Characterization of *hapR*, a positive regulator of the *Vibrio cholerae* HA/protease gene *hap*, and its identification as a functional homologue of the *Vibrio harveyi luxR* gene. Mol. Microbiol. **26:**1023–1034.
265. **Budarina ZI, Nikitin DV, Zenkin N, Zakharova M, Semenova E, Shlyapnikov MG, Rodikova EA, Masyukova S, Ogarkov O, Baida GE, Solonin AS, Severinov K.** 2004. A new *Bacillus cereus* DNA-binding protein, HlyIIR, negatively regulates expression of *B. cereus* haemolysin II. Microbiology **150:**3691–3701.
266. **Sandu C, Chiribau CB, Brandsch R.** 2003. Characterization of HdnoR, the transcriptional repressor of the 6-hydroxy-D-nicotine oxidase gene of *Arthrobacter nicotinovorans* pAO1, and its DNA-binding activity in response to L- and D-nicotine derivatives. J. Biol. Chem. **278:**51307–51315.
267. **Conlon KM, Humphreys H, O'Gara JP.** 2002. *icaR* encodes a transcriptional repressor involved in environmental regulation of *ica* operon expression and biofilm formation in *Staphylococcus epidermidis*. J. Bacteriol. **184:**4400–4408.
268. **Palumbo JD, Kado CI, Phillips DA.** 1998. An isoflavonoid-inducible efflux pump in *Agrobacterium tumefaciens* is involved in competitive colonization of roots. J. Bacteriol. **180:**3107–3113.
269. **Wang L, White RL, Vining LC.** 2002. Biosynthesis of the dideoxysugar component of jadomycin B: genes in the *jad* cluster of *Streptomyces venezuelae* ISP5230 for L-digitoxose assembly and transfer to the angucycline aglycone. Microbiology **148:**1091–1103.
270. **Yang K, Han L, Vining LC.** 1995. Regulation of jadomycin B production in *Streptomyces venezuelae* ISP5230: involvement of a repressor gene, *jadR2*. J. Bacteriol. **177:**6111–6117.
271. **Kharel MK, Nybo SE, Shepherd MD, Rohr J.** 2010. Cloning and characterization of the ravidomycin and chrysomycin biosynthetic gene clusters. Chembiochem **11:**523–532.
272. **Zhang H, White-Phillip JA, Melançon CE, Kwon HJ, Yu WL, Liu HW.** 2007. Elucidation of the kijanimicin gene cluster: insights into the biosynthesis of spirotetronate antibiotics and nitrosugars. J. Am. Chem. Soc. **129:**14670–14683.
273. **Gould SJ, Hong ST, Carney JR.** 1998. Cloning and heterologous expression of genes from the kinamycin biosynthetic pathway of *Streptomyces murayamaensis*. J. Antibiot. (Tokyo) **51:**50–57.
274. **Weber T, Laiple KJ, Pross EK, Textor A, Grond S, Welzel K, Pelzer S, Vente A, Wohlleben W.** 2008. Molecular analysis of the kirromycin biosynthetic gene cluster revealed beta-alanine as precursor of the pyridone moiety. Chem. Biol. **15:**175–188.
275. **Choi SU, Kim MK, Ha HS, Hwang YI.** 2008. *In vivo* functions of the gamma-butyrolactone autoregulator receptor in *Streptomyces ambofaciens* producing spiramycin. Biotechnol. Lett. **30:**891–897.
276. **Zhang X, Alemany LB, Fiedler HP, Goodfellow M, Parry RJ.** 2008. Biosynthetic investigations of lactonamycin and lactonamycin z: cloning of the biosynthetic gene clusters and discovery of an unusual starter unit. Antimicrob. Agents Chemother. **52:**574–585.
277. **Fidopiastis PM, Miyamoto CM, Jobling MG, Meighen EA, Ruby EG.** 2002. LitR, a new transcriptional activator in *Vibrio fischeri*, regulates luminescence and symbiotic light organ colonization. Mol. Microbiol. **45:**131–143.
278. **Si D, Urano N, Shimizu S, Kataoka M.** 2012. LplR, a repressor belonging to the TetR family, regulates expression of the L-pantoyl lactone dehydrogenase gene in *Rhodococcus erythropolis*. Appl. Environ. Microbiol. **78:**7923–7930.
279. **Miyamoto CM, Chatterjee J, Swartzman E, Szittner R, Meighen EA.** 1996. The role of lux autoinducer in regulating luminescence in *Vibrio harveyi*; control of *luxR* expression. Mol. Microbiol. **19:**767–775.
280. **Lin YH, Miyamoto C, Meighen EA.** 2000. Cloning and functional studies of a *luxO* regulator LuxT from *Vibrio harveyi*. Biochim. Biophys. Acta **1494:**226–235.
281. **de la Paz Santangelo M, Klepp L, Nuñez-García J, Blanco FC, Soria M, García-Pelayo MC, Bianco MV, Cataldi AA, Golby P, Jackson M, Gordon SV, Bigi F.** 2009. Mce3R, a TetR-type transcriptional repressor, controls the expression of a regulon involved in lipid metabolism in *Mycobacterium tuberculosis*. Microbiology **155:**2245–2255.
282. **Ichinose K.** 2003. Cloning, sequencing and heterologous expression of the medermycin biosynthetic gene cluster of *Streptomyces* sp. AM-7161: towards comparative analysis of the benzoisochromanequinone gene clusters. Microbiology **149:**1633–1645.
283. **Fukumori F, Hirayama H, Takami H, Inoue A, Horikoshi K.** 1998. Isolation and transposon mutagenesis of a *Pseudomonas putida* KT2442 toluene-resistant variant: involvement of an efflux system in solvent resistance. Extremophiles **2:**395–400.
284. **He M, Haltli B, Summers M, Feng X, Hucul J.** 2006. Isolation and characterization of meridamycin biosynthetic gene cluster from *Streptomyces* sp. NRRL 30748. Gene **377:**109–118.
285. **Chuanchuen R, Gaynor JB, Karkhoff-Schweizer R, Schweizer HP.** 2005. Molecular characterization of MexL, the transcriptional repressor of the *mexJK* multidrug efflux operon in *Pseudomonas aeruginosa*. Antimicrob. Agents Chemother. **49:**1844–1851.
286. **Westbrock-Wadman S, Sherman DR, Hickey MJ, Coulter SN, Zhu YQ, Warrener P, Nguyen LY, Shawar RM, Folger KR, Stover CK.** 1999. Characterization of a *Pseudomonas aeruginosa* efflux pump contributing to aminoglycoside impermeability. Antimicrob. Agents Chemother. **43:**2975–2983.
287. **O'Rourke S, Wietzorrek A, Fowler K, Corre C, Challis GL, Chater KF.** 2009. Extracellular signalling, translational control, two repressors and an activator all contribute to the regulation of methylenomycin production in *Streptomyces coelicolor*. Mol. Microbiol. **71:**763–778.
288. **Aguilar A, Hopwood DA.** 1982. Determination of methylenomycin A synthesis by the pSV1 plasmid from *Streptomyces violaceusruber* SANK 95570. J. Gen. Microbiol. **128:**1893–1901.
289. **Oliynyk M, Stark CB, Bhatt A, Jones MA, Hughes-Thomas ZA,**

Wilkinson C, Oliynyk Z, Demydchuk Y, Staunton J, Leadlay PF. 2003. Analysis of the biosynthetic gene cluster for the polyether antibiotic monensin in *Streptomyces cinnamonensis* and evidence for the role of *monB* and *monC* genes in oxidative cyclization. Mol. Microbiol. **49:** 1179–1190.

290. **Yang M, Gao C, Cui T, An J, He ZG.** 2012. A TetR-like regulator broadly affects the expressions of diverse genes in *Mycobacterium smegmatis*. Nucleic Acids. Res. **40:**1009–1020.
291. **Hagman KE, Shafer WM.** 1995. Transcriptional control of the *mtr* efflux system of *Neisseria gonorrhoeae*. J. Bacteriol. **177:**4162–4165.
292. **Cao L, Srikumar R, Poole K.** 2004. MexAB-OprM hyperexpression in NalC-type multidrug-resistant *Pseudomonas aeruginosa*: identification and characterization of the *nalC* gene encoding a repressor of PA3720-PA3719. Mol. Microbiol. **53:**1423–1436.
293. **Daigle DM, Cao L, Fraud S, Wilke MS, Pacey A, Klinoski R, Strynadka NC, Dean CR, Poole K.** 2007. Protein modulator of multidrug efflux gene expression in *Pseudomonas aeruginosa*. J. Bacteriol. **189:**5441–5451.
294. **Ghosh S, Cremers CM, Jakob U, Love NG.** 2011. Chlorinated phenols control the expression of the multidrug resistance efflux pump MexAB-OprM in *Pseudomonas aeruginosa* by interacting with NalC. Mol. Microbiol. **79:**1547–1556.
295. **Starr LM, Fruci M, Poole K.** 2012. Pentachlorophenol Induction of the *Pseudomonas aeruginosa mexAB-oprM* Efflux Operon: involvement of Repressors NalC and MexR and the Antirepressor ArmR. PLoS One **7:**e32684. doi:10.1371/journal.pone.0032684.
296. **Morita Y, Sobel ML, Poole K.** 2006. Antibiotic inducibility of the MexXY multidrug efflux system of *Pseudomonas aeruginosa*: involvement of the antibiotic-inducible PA5471 gene product. J. Bacteriol. **188:** 1847–1855.
297. **Winter JM, Moffitt MC, Zazopoulos E, McAlpine JB, Dorrestein PC, Moore BS.** 2007. Molecular basis for chloronium-mediated meroterpene cyclization: cloning, sequencing, and heterologous expression of the napyradiomycin biosynthetic gene cluster. J. Biol. Chem. **282:**16362–16368.
298. **Liu W, Nonaka K, Nie L, Zhang J, Christenson SD, Bae J, Van Lanen SG, Zazopoulos E, Farnet CM, Yang CF, Shen B.** 2005. The neocarzinostatin biosynthetic gene cluster from *Streptomyces carzinostaticus* ATCC 15944 involving two iterative type I polyketide synthases. Chem. Biol. **12:**293–302.
299. **Umezawa Y, Shimada T, Kori A, Yamada K, Ishihama A.** 2008. The uncharacterized transcription factor YdhM is the regulator of the *nemA* gene, encoding N-ethylmaleimide reductase. J. Bacteriol. **190:**5890–5897.
300. **Poole K, Gotoh N, Tsujimoto H, Zhao Q, Wada A, Yamasaki T, Neshat S, Yamagishi J, Li XZ, Nishino T.** 1996. Overexpression of the *mexC-mexD-oprJ* efflux operon in *nfxB*-type multidrug-resistant strains of *Pseudomonas aeruginosa*. Mol. Microbiol. **21:**713–724.
301. **Walczak RJ, Woo AJ, Strohl WR, Priestley ND.** 2000. Nonactin biosynthesis: the potential nonactin biosynthesis gene cluster contains type II polyketide synthase-like genes. FEMS Microbiol. Lett. **183:**171–175.
302. **Bililign T, Hyun CG, Williams JS, Czisny AM, Thorson JS.** 2004. The hedamycin locus implicates a novel aromatic PKS priming mechanism. Chem. Biol. **11:**959–969.
303. **Lombó F, Braña AF, Salas JA, Méndez C.** 2004. Genetic organization of the biosynthetic gene cluster for the antitumor angucycline oviedomycin in *Streptomyces antibioticus* ATCC 11891. Chembiochem **5:**1181–1187.
304. **Rost R, Haas S, Hammer E, Herrmann H, Burchhardt G.** 2002. Molecular analysis of aerobic phenylacetate degradation in *Azoarcus evansii*. Mol. Genet. Genomics **267:**656–663.
305. **Mast Y, Weber T, Gölz M, Ort-Winklbauer R, Gondran A, Wohlleben W, Schinko E.** 2011. Characterization of the 'pristinamycin supercluster' of *Streptomyces pristinaespiralis*. Microb. Biotechnol. **4:**192–206.
306. **Boutrin MC, Wang C, Aruni W, Li X, Fletcher HM.** 2012. Nitric oxide stress resistance in *Porphyromonas gingivalis* is mediated by a putative hydroxylamine reductase. J. Bacteriol. **194:**1582–1592.
307. **Metsä-Ketelä M, Ylihonko K, Mäntsälä P.** 2004. Partial activation of a silent angucycline-type gene cluster from a rubromycin beta producing *Streptomyces* sp. PGA64. J. Antibiot. (Tokyo) **57:**502–510.
308. **Bottiglieri M, Keel C.** 2006. Characterization of PhlG, a hydrolase that specifically degrades the antifungal compound 2,4-diacetylphloroglucinol in the biocontrol agent *Pseudomonas fluorescens* CHA0. Appl. Environ. Microbiol. **72:**418–427.
309. **Gristwood T, Fineran PC, Everson L, Salmond GP.** 2008. PigZ, a TetR/AcrR family repressor, modulates secondary metabolism via the expression of a putative four-component resistance-nodulation-cell-division efflux pump, ZrpADBC, in *Serratia* sp. ATCC 39006. Mol. Microbiol. **69:**418–435.
310. **Butcher RA, Schroeder FC, Fischbach MA, Straight PD, Kolter R, Walsh CT, Clardy J.** 2007. The identification of bacillaene, the product of the PksX megacomplex in *Bacillus subtilis*. Proc. Natl. Acad. Sci. U. S. A. **104:**1506–1509.
311. **Dürr C, Schnell HJ, Luzhetskyy A, Murillo R, Weber M, Welzel K, Vente A, Bechthold A.** 2006. Biosynthesis of the terpene phenalinolactone in *Streptomyces* sp. Tü6071: analysis of the gene cluster and generation of derivatives. Chem. Biol. **13:**365–377.
312. **Huang X, Zhu D, Ge Y, Hu H, Zhang X, Xu Y.** 2004. Identification and characterization of *pltZ*, a gene involved in the repression of pyoluteorin biosynthesis in *Pseudomonas* sp. M18. FEMS Microbiol. Lett. **232:**197–202.
313. **Vargas P, Felipe A, Michán C, Gallegos MT.** 2011. Induction of *Pseudomonas syringae* pv. tomato DC3000 MexAB-OprM multidrug efflux pump by flavonoids is mediated by the repressor PmeR. Mol. Plant Microbe Interact. **24:**1207–1219.
314. **Cho YH, Kim EJ, Chung HJ, Choi JH, Chater KF, Ahn BE, Shin JH, Roe JH.** 2003. The *pqrAB* operon is responsible for paraquat resistance in *Streptomyces coelicolor*. J. Bacteriol. **185:**6756–6763.
315. **Zhang X, Parry RJ.** 2007. Cloning and characterization of the pyrrolomycin biosynthetic gene clusters from *Actinosporangium vitaminophilum* ATCC 31673 and *Streptomyces* sp. strain UC 1106. Antimicrob. Agents Chemother. **51:**946–957.
316. **Huang T, Wang Y, Yin J, Du Y, Tao M, Xu J, Chen W, Lin S, Deng Z.** 2011. Identification and characterization of the pyridomycin biosynthetic gene cluster of *Streptomyces pyridomyceticus* NRRL B-2517. J. Biol. Chem. **286:**20648–20657.
317. **Hirooka K, Fujita Y.** 2011. Identification of aromatic residues critical to the DNA binding and ligand response of the *Bacillus subtilis* QdoR (YxaF) repressor antagonized by flavonoids. Biosci. Biotechnol. Biochem. **75:**1325–1334.
318. **Baucheron S, Coste F, Canepa S, Maurel MC, Giraud E, Culard F, Castaing B, Roussel A, Cloeckaert A.** 2012. Binding of the RamR repressor to wild-type and mutated promoters of the RamA gene involved in efflux-mediated multidrug resistance in *Salmonella enterica* serovar Typhimurium. Antimicrob. Agents Chemother. **56:**942–948.
319. **Heinzelmann E, Berger S, Müller C, Härtner T, Poralla K, Wohlleben W, Schwartz D.** 2005. An acyl-CoA dehydrogenase is involved in the formation of the delta cis3 double bond in the acyl residue of the lipopeptide antibiotic friulimicin in *Actinoplanes friuliensis*. Microbiology **151:**1963–1974.
320. **Jakobi K, Hertweck C.** 2004. A gene cluster encoding resistomycin biosynthesis in *Streptomyces resistomycificus*; exploring polyketide cyclization beyond linear and angucyclic patterns. J. Am. Chem. Soc. **126:** 2298–2299.
321. **Sun Y, Hahn F, Demydchuk Y, Chettle J, Tosin M, Osada H, Leadlay PF.** 2010. In vitro reconstruction of tetronate RK-682 biosynthesis. Nat. Chem. Biol. **6:**99–101.
322. **Hernández-Mendoza A, Nava N, Santana O, Abreu-Goodger C, Tovar A, Quinto C.** 2007. Diminished redundancy of outer membrane factor proteins in rhizobiales: a *nodT* homolog is essential for free-living *Rhizobium etli*. J. Mol. Microbiol. Biotechnol. **13:**22–34.
323. **González-Pasayo R, Martínez-Romero E.** 2000. Multiresistance genes of *Rhizobium etli* CFN42. Mol. Plant Microbe Interact. **13:**572–577.
324. **Kawasaki T, Sakurai F, Nagatsuka SY, Hayakawa Y.** 2009. Prodigiosin biosynthesis gene cluster in the roseophilin producer *Streptomyces griseoviridis*. J. Antibiot. (Tokyo) **62:**271–276.
325. **Ou X, Zhang B, Zhang L, Zhao G, Ding X.** 2009. Characterization of *rrdA*, a TetR family protein gene involved in the regulation of secondary metabolism in *Streptomyces coelicolor*. Appl. Environ. Microbiol. **75:** 2158–2165.
326. **Shimada T, Ishihama A, Busby SJ, Grainger DC.** 2008. The *Escherichia coli* RutR transcription factor binds at targets within genes as well as intergenic regions. Nucleic Acids Res. **36:**3950–3955.
327. **Bolla JR, Do SV, Long F, Dai L, Su CC, Lei HT, Chen X, Gerkey JE, Murphy DC, Rajashankar KR, Zhang Q, Yu EW.** 2012. Structural and functional analysis of the transcriptional regulator Rv3066 of *Mycobacterium tuberculosis*. Nucleic Acids Res. **40:**9340–9355.
328. **Choi SU, Lee CK, Hwang YI, Kinoshita H, Nihira T.** 2004. Cloning and

functional analysis by gene disruption of a gene encoding a gamma-butyrolactone autoregulator receptor from *Kitasatospora setae*. J. Bacteriol. **186:**3423–3430.
329. **Pan Y, Wang L, He X, Tian Y, Liu G, Tan H.** 2011. SabR enhances nikkomycin production via regulating the transcriptional level of *sanG*, a pathway-specific regulatory gene in *Streptomyces ansochromogenes*. BMC Microbiol. **11:**164.
330. **Healy FG, Eaton KP, Limsirichai P, Aldrich JF, Plowman AK, King RR.** 2009. Characterization of gamma-butyrolactone autoregulatory signaling gene homologs in the angucyclinone polyketide WS5995B producer *Streptomyces acidiscabies*. J. Bacteriol. **191:**4786–4797.
331. **Han S, Song P, Ren T, Huang X, Cao C, Zhang B.** 2011. Identification of SACE_7040, a member of TetR family related to the morphological differentiation of *Saccharopolyspora erythraea*. Curr. Microbiol. **63:**121–125.
332. **Duong CT, Lee HN, Choi SS, Lee SY, Kim ES.** 2009. Functional expression of SAV3818, a putative TetR-family transcriptional regulatory gene from *Streptomyces avermitilis*, stimulates antibiotic production in *Streptomyces* species. J. Microbiol. Biotechnol. **19:**136–139.
333. **Agari Y, Sakamoto K, Yutani K, Kuramitsu S, Shinkai A.** 2013. Structure and function of a TetR family transcriptional regulator, SbtR, from *Thermus thermophilus* HB8. Proteins **81:**1166–1178.
334. **Seipke RF, Song L, Bicz J, Laskaris P, Yaxley AM, Challis GL, Loria R.** 2011. The plant pathogen *Streptomyces scabies* 87-22 has a functional pyochelin biosynthetic pathway that is regulated by TetR- and AfsR-family proteins. Microbiology **157:**2681–2693.
335. **Basnet DB, Oh TJ, Vu TT, Sthapit B, Liou K, Lee HC, Yoo JC, Sohng JK.** 2006. Angucyclines Sch 47554 and Sch 47555 from *Streptomyces* sp. SCC-2136: cloning, sequencing, and characterization. Mol. Cells **22:**154–162.
336. **Rodríguez-García A, Combes P, Pérez-Redondo R, Smith MC, Smith MC.** 2005. Natural and synthetic tetracycline-inducible promoters for use in the antibiotic-producing bacteria *Streptomyces*. Nucleic Acids Res. **33:**e87.
337. **Okada U, Kondo K, Hayashi T, Watanabe N, Yao M, Tamura T, Tanaka I.** 2008. Structural and functional analysis of the TetR-family transcriptional regulator SCO0332 from *Streptomyces coelicolor*. Acta Crystallogr. D Biol. Crystallogr. **64:**198–205.
338. **Kim SH, Lee HN, Kim HJ, Kim ES.** 2011. Transcriptome analysis of an antibiotic downregulator mutant and synergistic actinorhodin stimulation via disruption of a precursor flux regulator in *Streptomyces coelicolor*. Appl. Environ. Microbiol. **77:**1872–1877.
339. **Xu D, Seghezzi N, Esnault C, Virolle MJ.** 2010. Repression of antibiotic production and sporulation in *Streptomyces coelicolor* by overexpression of a TetR family transcriptional regulator. Appl. Environ. Microbiol. **76:**7741–7753.
340. **Li L, Deng W, Song J, Ding W, Zhao QF, Peng C, Song WW, Tang GL, Liu W.** 2008. Characterization of the saframycin A gene cluster from *Streptomyces lavendulae* NRRL 11002 revealing a nonribosomal peptide synthetase system for assembling the unusual tetrapeptidyl skeleton in an iterative manner. J. Bacteriol. **190:**251–263.
341. **Olano C, Gómez C, Pérez M, Palomino M, Pineda-Lucena A, Carbajo RJ, Braña AF, Méndez C, Salas JA.** 2009. Deciphering biosynthesis of the RNA polymerase inhibitor streptolydigin and generation of glycosylated derivatives. Chem. Biol. **16:**1031–1044.
342. **Lee JH, Rhee JE, Park U, Ju HM, Lee BC, Kim TS, Jeong HS, Choi SH.** 2007. Identification and functional analysis of *Vibrio vulnificus* SmcR, a novel global regulator. J. Microbiol. Biotechnol. **17:**325–334.
343. **McDougald D, Rice SA, Kjelleberg S.** 2000. The marine pathogen *Vibrio vulnificus* encodes a putative homologue of the *Vibrio harveyi regulatory gene*, *luxR*: a genetic and phylogenetic comparison. Gene **248:**213–221.
344. **Sánchez P, Alonso A, Martinez JL.** 2002. Cloning and characterization of SmeT, a repressor of the *Stenotrophomonas maltophilia* multidrug efflux pump SmeDEF. Antimicrob. Agents Chemother. **46:**3386–3393.
345. **Chattoraj P, Mohapatra SS, Rao JL, Biswas I.** 2011. Regulation of transcription by SMU.1349, a TetR family regulator, in *Streptococcus mutans*. J. Bacteriol. **193:**6605–6613.
346. **Wu C, Cichewicz R, Li Y, Liu J, Roe B, Ferretti J, Merritt J, Qi F.** 2010. Genomic island TnSmu2 of *Streptococcus mutans* harbors a nonribosomal peptide synthetase-polyketide synthase gene cluster responsible for the biosynthesis of pigments involved in oxygen and H_2O_2 tolerance. Appl. Environ. Microbiol. **76:**5815–5826.
347. **Lee KM, Lee CK, Choi SU, Park HR, Kitani S, Nihira T, Hwang YI.** 2005. Cloning and in vivo functional analysis by disruption of a gene encoding the gamma-butyrolactone autoregulator receptor from *Streptomyces natalensis*. Arch. Microbiol. **184:**249–257.
348. **Lee K, Shimkets LJ.** 1994. Cloning and characterization of the *socA* locus which restores development to *Myxococcus xanthus* C-signaling mutants. J. Bacteriol. **176:**2200–2209.
349. **Folcher M, Gaillard H, Nguyen LT, Nguyen KT, Lacroix P, Bamas-Jacques N, Rinkel M, Thompson CJ.** 2001. Pleiotropic functions of a *Streptomyces pristinaespiralis* autoregulator receptor in development, antibiotic biosynthesis, and expression of a superoxide dismutase. J. Biol. Chem. **276:**44297–44306.
350. **Sun X, Zahir Z, Lynch KH, Dennis JJ.** 2011. An antirepressor, SrpR, is involved in transcriptional regulation of the SrpABC solvent tolerance efflux pump of *Pseudomonas putida* S12. J. Bacteriol. **193:**2717–2725.
351. **Wery J, Hidayat B, Kieboom J, de Bont JA.** 2001. An insertion sequence prepares *Pseudomonas putida* S12 for severe solvent stress. J. Biol. Chem. **276:**5700–5706.
352. **Arakawa K, Mochizuki S, Yamada K, Noma T, Kinashi H.** 2007. γ-Butyrolactone autoregulator-receptor system involved in lankacidin and lankamycin production and morphological differentiation in *Streptomyces rochei*. Microbiology **153:**1817–1827.
353. **Suzuki T, Mochizuki S, Yamamoto S, Arakawa K, Kinashi H.** 2010. Regulation of lankamycin biosynthesis in *Streptomyces rochei* by two SARP genes, *srrY* and *srrZ*. Biosci. Biotechnol. Biochem. **74:**819–827.
354. **Kitani S, Miyamoto KT, Takamatsu S, Herawati E, Iguchi H, Nishitomi K, Uchida M, Nagamitsu T, Omura S, Ikeda H, Nihira T.** 2011. Avenolide, a *Streptomyces* hormone controlling antibiotic production in *Streptomyces avermitilis*. Proc. Natl. Acad. Sci. U. S. A. **108:**16410–16415.
355. **Udwary DW, Zeigler L, Asolkar RN, Singan V, Lapidus A, Fenical W, Jensen PR, Moore BS.** 2007. Genome sequencing reveals complex secondary metabolome in the marine actinomycete *Salinispora tropica*. Proc. Natl. Acad. Sci. U. S. A. **104:**10376–10381.
356. **Carlson JC, Fortman JL, Anzai Y, Li S, Burr DA, Sherman DH.** 2010. Identification of the tirandamycin biosynthetic gene cluster from *Streptomyces* sp. 307-9. Chembiochem **11:**564–572.
357. **Jaques S, McCarter LL.** 2006. Three new regulators of swarming in *Vibrio parahaemolyticus*. J. Bacteriol. **188:**2625–2635.
358. **Engel P, Scharfenstein LL, Dyer JM, Cary JW.** 2001. Disruption of a gene encoding a putative gamma-butyrolactone-binding protein in *Streptomyces tendae* affects nikkomycin production. Appl. Microbiol. Biotechnol. **56:**414–419.
359. **Fang J, Zhang Y, Huang L, Jia X, Zhang Q, Zhang X, Tang G, Liu W.** 2008. Cloning and characterization of the tetrocarcin A gene cluster from *Micromonospora chalcea* NRRL 11289 reveals a highly conserved strategy for tetronate biosynthesis in spirotetronate antibiotics. J. Bacteriol. **190:**6014–6025.
360. **Guilfoile PG, Hutchinson CR.** 1992. The *Streptomyces glaucescens* TcmR protein represses transcription of the divergently oriented *tcmR* and *tcmA* genes by binding to an intergenic operator region. J. Bacteriol. **174:**3659–3666.
361. **Sosio M, Kloosterman H, Bianchi A, de Vreugd P, Dijkhuizen L, Donadio S.** 2004. Organization of the teicoplanin gene cluster in *Actinoplanes teichomyceticus*. Microbiology **150:**95–102.
362. **Tovar K, Ernst A, Hillen W.** 1988. Identification and nucleotide sequence of the class E *tet* regulatory elements and operator and inducer binding of the encoded purified Tet repressor. Mol. Gen. Genet. **215:**76–80.
363. **Navarro-Llorens JM, Drzyzga O, Perera J.** 2008. Genetic analysis of phenylacetic acid catabolism in *Arthrobacter oxydans* CECT386. Arch. Microbiol. **190:**89–100.
364. **Demirev AV, Khanal A, Hanh NP, Nam KT, Nam DH.** 2011. Biochemical characteristization of propionyl-coenzyme a carboxylase complex of *Streptomyces toxytricini*. J. Microbiol. **49:**407–412.
365. **Demydchuk Y, Sun Y, Hong H, Staunton J, Spencer JB, Leadlay PF.** 2008. Analysis of the tetronomycin gene cluster: insights into the biosynthesis of a polyether tetronate antibiotic. Chembiochem **9:**1136–1145.
366. **Nash KA, Andini N, Zhang Y, Brown-Elliott BA, Wallace RJ.** 2006. Intrinsic macrolide resistance in rapidly growing mycobacteria. Antimicrob. Agents Chemother. **50:**3476–3478.
367. **Mo X, Wang Z, Wang B, Ma J, Huang H, Tian X, Zhang S, Zhang C, Ju J.** 2011. Cloning and characterization of the biosynthetic gene cluster of the bacterial RNA polymerase inhibitor tirandamycin from marine-

derived *Streptomyces* sp. SCSIO1666. Biochem. Biophys. Res. Commun. **406:**341–347.
368. **Teran W, Felipe A, Segura A, Rojas A, Ramos L, Gallegos T.** 2003. Antibiotic-dependent induction of *Pseudomonas putida* DOT-T1E TtgABC efflux pump Is mediated by the drug binding repressor TtgR. Antimicrob. Agents Chemother. **47:**3067–3072.
369. **Terán W, Krell T, Ramos JL, Gallegos MT.** 2006. Effector-repressor interactions, binding of a single effector molecule to the operator-bound TtgR homodimer mediates derepression. J. Biol. Chem. **281:**7102–7109.
370. **Rojas A, Segura A, Guazzaroni ME, Terán W, Hurtado A, Gallegos MT, Ramos JL.** 2003. In vivo and in vitro evidence that TtgV is the specific regulator of the TtgGHI multidrug and solvent efflux pump of *Pseudomonas putida*. J. Bacteriol. **185:**4755–4763.
371. **Preiter K, Brooks DM, Penaloza-Vazquez A, Sreedharan A, Bender CL, Kunkel BN.** 2005. Novel virulence gene of *Pseudomonas syringae* pv. tomato strain DC3000. J. Bacteriol. **187:**7805–7814.
372. **Bignell DR, Bate N, Cundliffe E.** 2007. Regulation of tylosin production: role of a TylP-interactive ligand. Mol. Microbiol. **63:**838–847.
373. **Stratigopoulos G, Gandecha AR, Cundliffe E.** 2002. Regulation of tylosin production and morphological differentiation in *Streptomyces fradiae* by TylP, a deduced gamma-butyrolactone receptor. Mol. Microbiol. **45:**735–744.
374. **Novel M, Novel G.** 1976. Regulation of beta-glucuronidase synthesis in *Escherichia coli* K-12: constitutive mutants specifically derepressed for *uidA* expression. J. Bacteriol. **127:**406–417.
375. **Croxatto A, Chalker VJ, Lauritz J, Jass J, Hardman A, Williams P, Cámara M, Milton DL.** 2002. VanT, a homologue of *Vibrio harveyi* LuxR, regulates serine, metalloprotease, pigment, and biofilm production in *Vibrio anguillarum*. J. Bacteriol. **184:**1617–1629.
376. **Borges-Walmsley MI, Du D, McKeegan KS, Sharples GJ, Walmsley AR.** 2005. VceR regulates the *vceCAB* drug efflux pump operon of *Vibrio cholerae* by alternating between mutually exclusive conformations that bind either drugs or promoter DNA. J. Mol. Biol. **349:**387–400.
377. **Garg RP, Ma Y, Hoyt JC, Parry RJ.** 2002. Molecular characterization and analysis of the biosynthetic gene cluster for the azoxy antibiotic valanimycin. Mol. Microbiol. **46:**505–517.
378. **Hasegawa H, Häse CC.** 2009. TetR-type transcriptional regulator VtpR functions as a global regulator in *Vibrio tubiashii*. Appl. Environ. Microbiol. **75:**7602–7609.

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