

Comparative Analysis of Two-component Signal Transduction System in Two Streptomyces Genomes

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Abstract Species of the genus *Streptomyces* are major bacteria responsible for producing most natural antibiotics. *Streptomyces coelicolor* A3(2) and *Streptomyces avermitilis* were sequenced in 2002 and 2003, respectively. Two-component signal transduction systems (TCSs), consisting of a histidine sensor kinase (SK) and a cognate response regulator (RR), form the most common mechanism of transmembrane signal transduction in prokaryotes. TCSs in *S. coelicolor* A3(2) have been analyzed in detail. Here, we identify and classify the SK and RR of *S. avermitilis* and compare the TCSs with those of *S. coelicolor* A3(2) by computational approaches. Phylogenetic analysis of the cognate SK-RR pairs of the two species indicated that the cognate SK-RR pairs fall into four classes according to the distribution of their orthologs in other organisms. In addition to the cognate SK-RR pairs, some potential partners of non-cognate SK-RR were found, including those of unpaired SK and orphan RR and the cross-talk between different components in either strain. Our study provides new clues for further exploration of the molecular regulation mechanism of streptomycetes with industrial importance.

Key words *Streptomyces*; two-component system; cross-talk; phylogenetic analysis

Two-component signal transduction systems (TCSs), consisting of a histidine (His) sensor kinase (SK) and a cognate response regulator (RR), serve as a basic stimulus-response coupling mechanism to allow organisms to sense and respond to changes in many different environmental conditions in prokaryotes [1]. They are widespread not only in almost all prokaryotes and many archaea, but also in some eukaryotes, such as fungi and plants, in which they play an important role in light and hormone signaling.

Most of the SKs are membrane-associated His kinases. Extracellular stimuli are sensed by the periplasmic domain of the SK, and serve to modulate the activities of the SK. The SK catalyzes ATP-dependent autophosphorylation of a specific His residue located in its dimerization domain. The phosphoryl group subsequently transfers from the phosphohistidine of the SK to a specific aspartate (Asp) residue within the conserved regulatory domain of the RR. Phosphorylation of the regulatory domain activates a downstream output domain that elicits the specific cellular response [2].

Streptomyces is a genus of Gram-positive bacteria. Unlike normal bacteria, streptomycetes have a complex development life cycle such as mycelial growth and spore formation. To adapt the particularly complex and variable environment, streptomycetes possess a broad range of metabolic processes and biotransformations [3,4]. The

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most interesting property of streptomycetes is their ability to produce most natural antibiotics used in human and veterinary medicine and agriculture. Therefore it is quite essential to understand the biological process of remarkable morphological differentiation and antibiotic production in streptomycetes [5]. Over 20 different pleiotropic genes influence antibiotic production in *Streptomyces coelicolor* A3(2), three of which are TCSs, indicating an important role for protein phosphorylation and phosphorylation cascades in the regulation of antibiotic production [6].

Two complete genomic sequences of the genus *Streptomyces* are now available. *S. coelicolor* A3(2), the best-known representative of streptomycetes, was sequenced in 2002 and has an 8.7 Mbp linear chromosome containing 7825 protein-encoding sequences [3,4]. The second streptomycete genome, *S. avermitilis*, was published in 2003 [4]. The linear chromosome of this genome is just over 9 Mbp, which is larger than that of *S. coelicolor* A3(2) but contains fewer open reading frames (7574 instead of 7825). Comparative analysis of the two streptomycete genomes revealed that there is a common highly conserved 6.5 Mbp region with respect to gene order and content [4]. SKs and RRs of *S. coelicolor* A3(2) have been analyzed in detail [7]. However, to date, a detailed analysis of TCSs of *S. avermitilis* has not been reported.

In this study, we attempt to conduct a comparative analysis that will constitute a basis for further exploration of the signal transduction systems of streptomycetes.

Materials and Methods

Identification and classification of SKs and RRs of *S. avermitilis*

The genome sequences of *S. avermitilis* (<http://avermitilis.ls.kitasono-u.ac.jp/>) were searched against the Interpro database [8] using InterproScan on a local workstation. The SKs were identified by visual inspection of all the proteins that contain the ATPase domain [7,10]. According to the alignments of the 16 amino acids around the conserved histidine for each of the five groups of SKs in *Bacillus subtilis* [11], we made five hidden Markov models (HMMs) using the hmmbuild program of the HMMER package Version 2.3.2 [12] (<http://hmmer.janelia.org/>). The identified SKs were assigned to five groups by searching the five HMMs using the hmmpfam program of the HMMER suite ($E < 10^{-5}$). The transmembrane (TM) domains of each SK were acquired using TopPred II (<http://bioweb.pasteur.fr/seqanal/interfaces/toppred.html>) [13].

The two best matches for each SK were assumed to be the true TM domains, and all the residues between the end of the first and the start of the second TM domain were taken as the sensor domain. Similar to SKs, RRs were identified by checking all the proteins that contain the CheY-like domain. Alignments of the C-terminal output domains of *S. avermitilis* RRs with those of *Escherichia coli* RRs revealed the five different groups of RRs [11]. All the functional domains of SKs and RRs were obtained from the InterproScan results.

Comparison of TCSs in *S. coelicolor* A3(2) and *S. avermitilis*

All the orthologs of the TCSs were retrieved through KEGG API (<http://www.genome.jp/kegg/soap/>; SOAP interface to KEGG) from KEGG SSDB using best-best relations (Smith-Waterman score > 100). The orthologs of SKs in the two streptomycete genomes with less than 50% amino acid sequence identity in their sensor domains were ignored.

Sequence alignment and phylogenetic analysis

In addition to trans-phosphorylation between cognate SK-RR pairs, cross-talk in trans-phosphorylation between non-adjacent SK-RR pairs was also reported [14]. To explore those potential cross-talks in *S. coelicolor* A3(2) and *S. avermitilis*, we inferred functional coupling between SKs and RRs based on conservation of SK-RR pairs between genomes, which is employed as a classical computational method to predicting functionally coupled genes [15]. If orthologs of non-cognate SK and RR in *S. coelicolor* A3(2) and *S. avermitilis* are adjacent in some other organisms, we assumed that the potential cross-talk in signal transduction might take place between them or they are a potential pair (Fig. 1). We took those non-cognate SK and RR pairs with more than 10 support ortholog pairs in other organisms as the potential pairs or the potential cross-talks of TCSs in either streptomycete genomes. The multiple alignments were obtained by aligning with the program CLUSTAL W [16] and phylogenetic trees were constructed using PHYLIP based on the neighbor-joining algorithm [17] and the bootstrap value was 1000.

Results

Identification of TCSs of *S. avermitilis* and comparison with *S. coelicolor* A3(2)

Sixty-seven SKs were obtained after the visual inspection

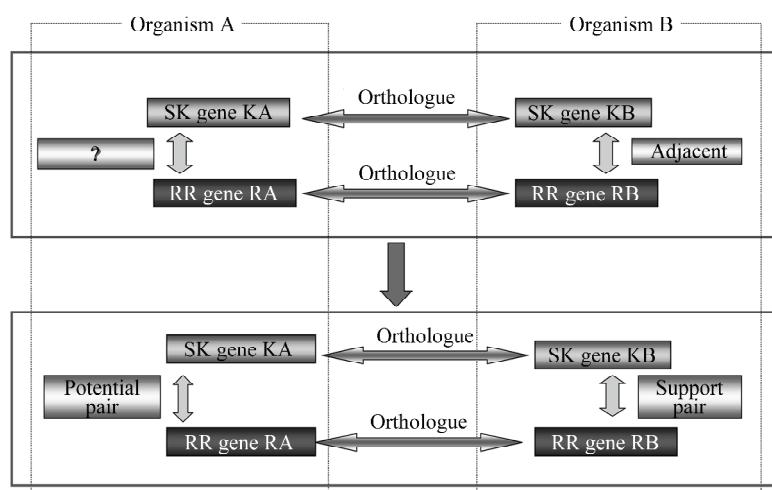


Fig. 1 Method used in phylogenetic analysis of two-component signal transduction system pairs

If the histidine sensor kinase (SK), assigned as KB (ortholog of KA), and the response regulator (RR), assigned as RB (ortholog of RA), are cognate SK-RR pairs in some other organisms, we assumed that KA and RA are potential pairs, and the KB-RB pairs were taken as support pairs.

of *S. avermitilis* proteins that contain both the ATPase domain and the conserved His domain. Similarly, 68 RRs were found by checking the CheY-like domain and the RR output domain. Of these 67 SKs, 53 are adjacent to RRs (one pair is assumed), and 14 are unpaired. Besides the 53 paired RRs, there are 15 orphan RRs as well (**Table 1**).

The sensor domains of SKs vary greatly to sense diverse environment stimuli, and the ATP domains, conserved in all SKs, do little to differentiate them. The region around the conserved His, the site of autophosphorylation, proved to be more informative for classification of SKs. Alignment with the region around the His that becomes phosphorylated revealed that the SKs of *S. avermitilis* fell into the five main groups (I, II, IIIa, IIIb and IV), as defined in *B. subtilis* [11]. Similar to *S. coelicolor* A3(2), most of the SKs of the *S. avermitilis* fell into group II and IIIa (32 and 30, respectively), with only one in group I, one in group IIIb and five in group IV. The RRs were classified to NarL, OmpR, DBD, LytTR and wHtH groups by the relatedness of their output domains (**Table 1**). The largest number of RRs fell into the NarL group, which are all contain the bacterial regulatory protein LuxR domain (InterPro IPR000792). It was found that the second largest number of RRs containing the C-terminal transcriptional regulatory domain (Trans_reg_C; IPR001867) was related to the OmpR group. LuxR domain and the C-terminal transcriptional regulatory domain are subfamilies of winged helix repressor DNA-binding domain (IPR011991), which contains the winged helix-turn-helix DNA-binding motif. It is notable that SAV6219 contains the ANTAR domain

(IPR005561), which is an RNA-binding domain found in bacterial transcription antitermination regulatory proteins [18]. This domain has been detected in various RRs of TCSs and also some one-component sensory regulators from a variety of bacteria. Most activated RRs interact with DNA to activate or repress the transcription of a series of genes, however, ANTAR-containing RR might interact with RNA to resist the termination of special gene transcription.

It is interesting that, as in *B. subtilis* and *S. coelicolor* A3(2), all of the SKs in group II are linked with RRs classified as NarL family, whereas all of the group IIIa SKs are paired with RRs belonging to the OmpR family without exception. Two SKs of group IV are paired with RRs containing a typical winged helix-turn-helix domain, while the SKs of group I and IIIb are unpaired. The conclusion for the conserved relationship is that the catalytic domain of the SKs and both domains of the RRs might have evolved as a unit from a common ancestor [11]. Consistent with this conclusion, the gene orders of SK and RR in the transcription units are preserved within different classes (**Table 1**).

Most SKs contain a variety of extracellular, intracellular and/or transmembrane functional domains to respond to specific environmental stimuli. As a result, there is little sequence similarity in the N-terminal domains of the SKs. The membrane topology predictions of the SKs indicate that over half of the SKs have three or more TM domains. Three soluble cytoplasmic proteins were predicted for those SKs that contain no TM domain. They might be activated

Table 1 Classification and novel domains of the two-component signal transduction system in *Streptomyces avermitilis*

SK	Domain	Group	TM domain	SD length (aa)	RR	Domain	Group	Gene order
SAV7118	None	I	3-23,197-217	174	Unpaired	-	-	-
SAV932	None	II	72-92,149-169	57	SAV931	LuxR	NarL	HR
SAV1281	None	II	87-107,114-134	7	SAV1282	LuxR	NarL	RH
SAV1465	None	II	107-127,130-150	3	SAV1464	LuxR	NarL	HR
SAV1990	None	II	169-189,218-238	29	SAV1988	LuxR	NarL	HR
SAV2059	None	II	71-91,133-153	42	Unpaired	-	-	-
SAV2439	None	II	53-73,81-101	8	SAV2438	LuxR	NarL	HR
SAV2876	None	II	113-133,137-157	4	SAV2877	LuxR	NarL	HR
SAV3133	None	II	43-63,74-94	11	SAV3132	LuxR	NarL	HR
SAV3250	None	II	130-150,191-211	41	SAV3249	LuxR	NarL	HR
SAV3471	None	II	57-77,105-125	28	SAV3470	LuxR	NarL	HR
SAV3560	None	II	49-69,109-129	40	Unpaired	-	-	-
SAV3631	None	II	50-70,173-193	103	SAV3630	LuxR	NarL	HR
SAV4144	None	II	115-135,166-186	31	SAV4145	LuxR	NarL	HR
SAV4257	GAF	II	335-355	? †	Unpaired	-	-	-
SAV4453	None	II	23-43,48-68	5	SAV4454	LuxR	NarL	HR
SAV4534	None	II	154-174,205-225	31	SAV4535	LuxR	NarL	HR
SAV4536	None	II	106-126,204-224	78	SAV4537	LuxR	NarL	HR
SAV4680	None	II	17-37,135-155	98	SAV4681	LuxR	NarL	HR
SAV4879	None	II	63-83,201-221	118	SAV4878	LuxR	NarL	HR
SAV4880	None	II	52-72,148-168	76	Unpaired	-	-	-
SAV5604	None	II	56-76,147-167	71	SAV5605	LuxR	NarL	HR
SAV5623	None	II	15-35,124-144	89	SAV5624	LuxR	NarL	HR
SAV5719	GAF	II	279-299	? †	Unpaired	-	-	-
SAV5746	None	II	181-201,219-239	18	SAV5747	LuxR	NarL	HR
SAV5869	None	II	51-71,127-147	56	SAV5868	LuxR	NarL	HR
SAV5992	None	II	36-56,170-190	114	SAV5991	LuxR	NarL	HR
SAV6038	None	II	49-69,120-140	51	SAV6039	LuxR	NarL	HR
SAV6081	None	II	45-65,101-121	36	SAV6082	LuxR	NarL	HR
SAV6476	GAF	II	none	none	SAV6477	LuxR	NarL	HR
SAV7072	None	II	100-120,143-163	23	SAV7071	LuxR	NarL	HR
SAV7391	None	II	58-78,85-105	7	SAV7392	LuxR	NarL	HR
SAV28	None	IIIa	272-292	? †	Unpaired	-	-	-
SAV72	None	IIIa	60-80,229-249	149	SAV73	Trans_reg_C	OmpR	RH
SAV129	None	IIIa	17-37,158-178	121	SAV128	Trans_reg_C	OmpR	RH
SAV134	None	IIIa	8-28,142-162	114	Unpaired	-	-	-
SAV647	None	IIIa	136 - 156	? †	SAV648	Trans_reg_C	OmpR	RH
SAV1085	GAF	IIIa	715 - 735	? †	Unpaired	-	-	-
SAV2196	None	IIIa	18-38,159-179	121	SAV2195	Trans_reg_C	OmpR	RH
SAV2256	None	IIIa	14-34,167-187	133	SAV2257	Trans_reg_C	OmpR	RH
SAV2396	KdpD, Usp	IIIa	408-428,456-476	28	SAV2395	Trans_reg_C	OmpR	HR
SAV2404	None	IIIa	39-59,122-142	63	SAV2405	Trans_reg_C	OmpR	RH
SAV2482	None	IIIa	5-25,172-192	147	SAV2483	Trans_reg_C	OmpR	RH

To be continued

Continued

SK	Domain	Group	TM domain	SD length (aa)	RR	Domain	Group	Gene order
SAV2512	GAF	IIIa	1142-1162	? †	SAV2511	DBD	-	HR
SAV2950	None	IIIa	25-45,146-166	101	Unpaired	-	-	-
SAV2971	None	IIIa	27-47,54-74	7	SAV2970	Trans_reg_C	OmpR	RH
SAV3353	None	IIIa	31-51,197-217	146	SAV3352	Trans_reg_C	OmpR	RH
SAV3410	None	IIIa	22-42,180-200	138	SAV3409	Trans_reg_C	OmpR	RH
SAV3480	None	IIIa	7-27,125-145	98	SAV3481	Trans_reg_C	OmpR	RH
SAV3973	None	IIIa	6-26	? †	SAV3972	Trans_reg_C	OmpR	HR
SAV4048	None	IIIa	20-40,181-201	141	SAV4047	Trans_reg_C	OmpR	RH
SAV4158	None	IIIa	9-29,172-192	143	SAV4159	Trans_reg_C	OmpR	RH
SAV4197	None	IIIa	25-45,208-228	163	SAV4198	Trans_reg_C	OmpR	RH
SAV4417	None	IIIa	4-24,44-64	20	SAV4416	Trans_reg_C	OmpR	RH
SAV4703	None	IIIa	63-83,185-205	102	SAV4704	Trans_reg_C	OmpR	RH
SAV4768	None	IIIa	24-44,184-204	140	SAV4767	Trans_reg_C	OmpR	RH
SAV5064	None	IIIa	76-96,267-287	171	SAV5063	Trans_reg_C	OmpR	RH
SAV5251	None	IIIa	8-28,147-167	119	SAV5250	Trans_reg_C	OmpR	RH
SAV5564	GAF	IIIa	1164-1184	? †	SAV5563	-	DBD	HR
SAV5655	None	IIIa	5-25,164-184	139	SAV5656	Trans_reg_C	OmpR	RH
SAV6774	None	IIIa	32-52,193-213	141	SAV6773	Trans_reg_C	OmpR	RH
SAV6741	PAS	IIIb	none	none	Unpaired	-	-	-
SAV646	None	IV	153-173	? †	Unpaired	-	-	-
SAV2430	PAS	IV	27-47,178-198	131	SAV2431	-	wHtH	HR
SAV2816	PAS	IV	18-38,173-193	135	SAV2817	-	wHtH	HR
SAV3017	None	IV	none	none	Unpaired	-	-	-
SAV6889	NIT	IV	41-61,336-356	275	Unpaired	-	-	-
					SAV139	Trans_reg_C	OmpR	-
					SAV1612	Trans_reg_C	OmpR	-
					SAV2230	LuxR	NarL	-
					SAV2371	LuxR	NarL	-
					SAV2435	-	wHtH	-
					SAV3572	LuxR	NarL	-
					SAV3581	LuxR	NarL	-
					SAV4042	Trans_reg_C	OmpR	-
					SAV4375	LuxR	NarL	-
					SAV4998	LuxR	NarL	-
					SAV5068	LuxR	NarL	-
					SAV6219	ANTAR	-	-
					SAV6671	LuxR	NarL	-
					SAV7115	LytTR	LytTR	-
					SAV7499	LuxR	NarL	-

† Sensor domain was not identified by the transmembrane analysis. ANTAR, AmiR and NasR transcription antitermination regulators domain; DBD, no DNA binding domain; GAF, GAF domain; KdpD, osmosensitive K⁺ channel His kinase sensor domain; LuxR, LuxR domain; LytTR, LytTr DNA-binding region domain; NIT, Nitrate and nitrite sensing domain; PAS, PAS domain; RR, response regulator; SD, sensor domain; SK, histidine sensor kinase; TM, transmembrane domain; Trans_reg_C, C-terminal transcriptional regulatory protein domain; Usp, UspA domain; wHtH, winged helix-turn-helix. The TM column shows the position of the two best matches for each SK as the true TM predicted by TopPred II analysis. HR or RH refers to the gene order of the RR and SK in the transcriptional unit from the 5' end to the 3' end.

by another SK in the transduction pathway, as for *E. coli* CheA [19]. The region between the end of the first and the start of the second TM domain was taken as the sensor domain (**Table 1**). The size of the sensor domains ranges from 3 to 275 amino acids. Eight SKs containing sensor domains of less than 20 amino acids were predicted to belong to a new subfamily of SKs, which is almost entirely buried in the cytoplasmic membrane and frequently linked to ABC transporters. SKs of this new subfamily were speculated to sense changes in membrane structure or topology [20].

PAS and GAF domains, as cytosolic sensing modules, have been found in a large number of SKs. Three SKs that contain PAS domain (IPR000014) were found in the *S. avermitilis* genome. PAS domain proteins function to detect some signals, such as oxygen, redox potential and light, by binding flavins, haems, chromophores or some other cofactors [21]. The GAF domain (IPR003018) is found in six SKs of *S. avermitilis*. GAF domains appear to act as binding sites for small ligands that induce the autophosphorylation of the SK and subsequent signal transduction to activate specific gene transcription [22]. One SK (SAV6889) was detected that contains the nitrate and nitrite-sensing domain (IPR010910), which responds to changes in nitrate and nitrite concentrations.

Phylogenetic analysis of the TCSs in *S. avermitilis* and *S. coelicolor* A3(2) genomes

All the potential pairs of the TCSs in two streptomycete genomes were analyzed and the numbers of all supported pairs of each potential pair were counted. The organism distribution of each cognate SK-RR pair and the support pairs consisting of their orthologs showed that the paired TCSs fell into four classes: present in most bacteria; present in most actinobacteria; specific to streptomycetes; and specific to either of the two streptomycete strains.

KdpD-KdpE of *S. coelicolor* A3(2), have orthologs in *S. avermitilis* and 45 other bacteria. KdpD and KdpE, which regulate the expression of the high affinity K⁺ transport system most notably under K⁺ limiting conditions [23], have been extensively studied in *E. coli* and appear to be ubiquitous in most bacteria. Independent phylogenetic analyses were carried out using amino acid sequences of the regions assigned for classification of KdpD, KdpE and their orthologs (**Fig. 2**). The similarity of the two phylogenetic trees could imply the inherent functional connection between the catalytic domain of the SKs and both the regulatory and output domains of the RRs.

In the *S. coelicolor* A3(2) genome, 12 pairs of TCSs are present in most actinobacteria, and 42 TCS pairs are

specific to streptomycetes. CutRS, which might play roles in the production of actinorhodin [24], and ChiRS, which is related to chitinase production [25], might be specific to streptomycete strains. The TCS pairs specific in streptomycetes exceed more than those present in most bacteria or in the actinobacteria group, suggesting that this genus might be well equipped to adapt to a wide range of environmental stimuli and stresses, and to regulate complex multicellular development, a broad range of metabolic processes and biotransformation.

Phylogenetic analysis using all orthologs of available organisms revealed that 26 pairs of TCSs are specific to *S. coelicolor* A3(2). As mentioned above, the *S. coelicolor* A3(2) genome contains 31 paired TCSs that are specific compared to the *S. avermitilis* genome. Of these paired TCSs, five have orthologs in some other organisms but not in *S. avermitilis*. While in the 17 paired TCSs specific to *S. avermitilis*, only one pair has orthologs in other bacteria.

Discussion

The basic TCS elements can be combined to produce a His-Asp-His-Asp phosphorelay. Central to this phosphorelay pathway is a hybrid-type SK that contains both an SK core and an RR receiver domain in a single protein [26]. Two hybrid-type SKs and their orthologs (SAV1085 with SCO7327, SAV2512 with SCO5748) were identified in *S. avermitilis* and *S. coelicolor* A3(2). The third hybrid-type SK in *S. avermitilis*, SAV 5564, has no ortholog in *S. coelicolor* A3(2). The complexity of phosphorelay systems permits the integration of multiple check points and regulatory steps into the pathway [27].

In addition to the cognate TCS pairs we have discussed in detail, some potential pairs that are not adjacent in the genome were found by the ortholog analysis. The SK SAV1990 and RR SAV1988 are not back-to-back in the *S. avermitilis* genome. However, our analysis suggested that they are cognate, as their orthologs (SCO6253 and SCO6254) are adjacent and they accord with the rule that all SKs falling into group II are linked with an RR classified to the NarL family (**Table 1**). Orthologs of *S. avermitilis* TCSs, SAV7118 (SK) and SAV7115 (RR) are adjacent in 47 organisms (**Table 2**), and orthologs of SAV3017 (SK) and SAV6219 (RR) are adjacent in 10 organisms. These four TCSs had been supposed to be unpaired SKs or orphan RRs in *S. avermitilis* because they did not have an adjacent pair in the genome, but the cases in other organisms indicated that they might be two paired TCSs.

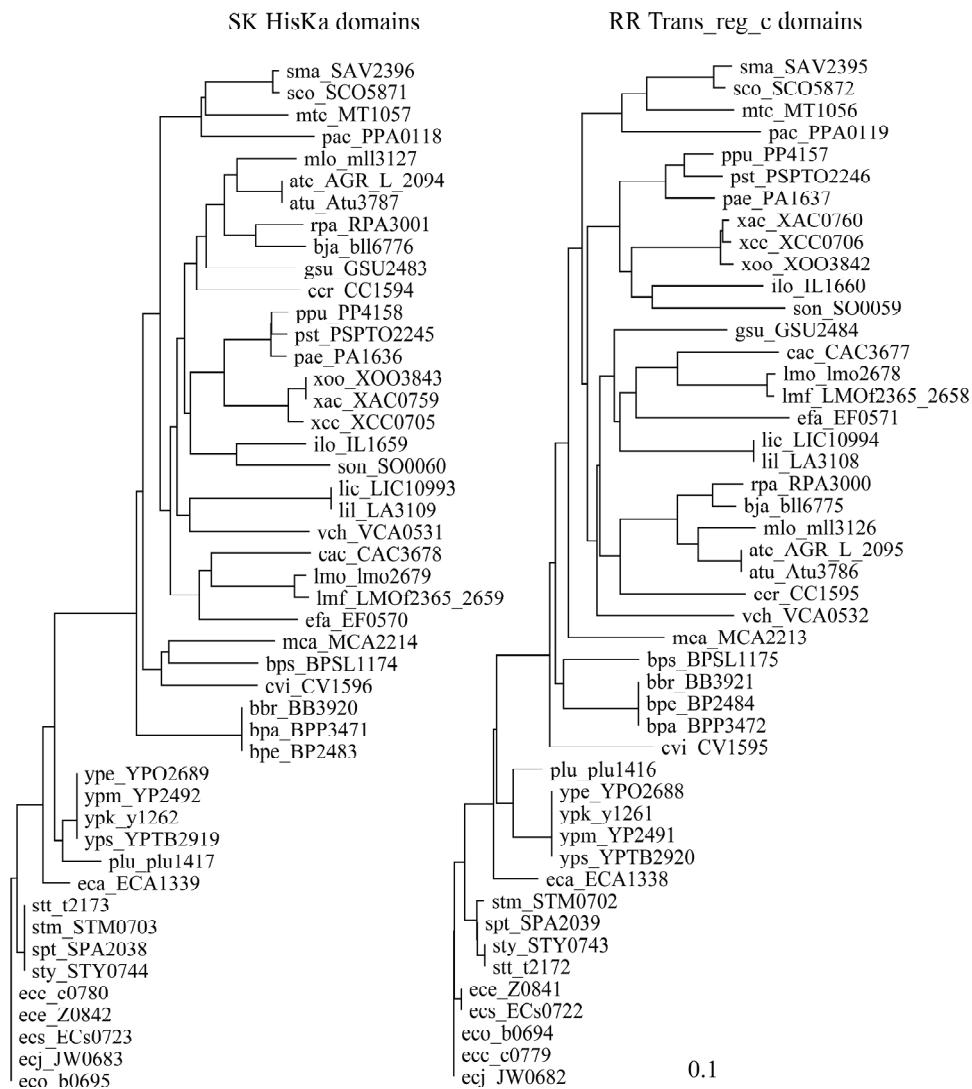


Fig. 2 Phylogenetic analysis of the histidine sensor kinase (SK) HisKa domains of all KdpD orthologs and the cognate response regulator (RR) Trans_reg_c domains of all KdpE orthologs

The domain sequences are indicated by the abbreviation of the species name (according to KEGG: http://www.genome.ad.jp/kegg/catalog/org_list.html) and protein ID. The scale bar represents 0.1 expected amino acid replacements per site in both phylogenetic analyses.

Microarray analysis for the TCS mutants of *E. coli* has represented that TCSs functionally interact with each other, at least for certain combinations, to expand the signal transduction network so as to allow some genes to respond to a wide range of environmental stimuli [28]. Trans-phosphorylation *in vitro* was detected between non-cognate SK-RR pairs in *E. coli* at a rate of approximately 3% [14], raising the possibility that the cross-talk in signal transduction takes place between non-cognate SKs and RRs. In this study, some non-cognate SK-RR pairs were found in both the *S. avermitilis* and *S. coelicolor* A3(2) genomes that have cognate ortholog SK-RR pairs in other

organisms (Table 2), suggesting that cross-talk might take place between them. TCSs, such as SCO7534, SCO3741, SCO1136 and SCO1801 in *S. coelicolor* A3(2), and SAV2430, SAV2971, SAV4416 and SAV4047 in *S. avermitilis* might be inclined to take part in the cross-talk. The streptomycete strain-specific TCSs have insufficient support pairs, so that the cross-talk referencing to these TCSs might be omitted. While our results accord with the corollary that if cross-talk between SK-RR pairs is of regulatory significance, it is likely to occur only within a group [11].

The identification and classification of the TCSs in the

Table 2 Potential pair or potential cross-talk between two-component signal transduction systems of *Streptomyces coelicolor* A3(2) and *Streptomyces avermitilis*

	SK	Group	RR	Group	Support pair number	Paired (P) or Cross-talk (C)
<i>S. coelicolor</i> A3(2)	SCO4229	IIIa	SCO3741	OmpR	31	C
	SCO5435	IV	SCO1136	wHtH	18	C
	SCO2142	IIIa	SCO4156	OmpR	18	C
	SCO7534	IIIa	SCO3013	OmpR	14	C
	SCO5829	IV	SCO1136	wHtH	13	C
	SCO0203	II	SCO3008	atypical [†]	11	C
<i>S. avermitilis</i>	SAV7118	I	SAV7115	LytTR	47	P
	SAV3973	IIIa	SAV4416	OmpR	32	C
	SAV2430	IV	SAV2435	wHtH	15	C
	SAV2971	IIIa	SAV5063	OmpR	14	C
	SAV2196	IIIa	SAV4047	OmpR	12	C
	SAV2404	IIIa	SAV4047	OmpR	10	C
	SAV3017	IV	SAV6219	ANTAR	10	P
	SAV3133	II	SAV5868	NarL	10	C

[†] The RR was not able to be classified to any typical group, such as OmpR, NarL, wHtH and so on. ANTAR, AmiR and NasR transcription antitermination regulators domain; LytTR, LytTr DNA-binding region domain; RR, response regulator; SK, histidine sensor kinase; wHtH, winged helix-turn-helix.

S. avermitilis genome provide the foundation to understand the signal transduction system of the strain. Approximately 80% of the commercially available antibiotics are produced by the streptomycetes, therefore comparison analysis of the TCSs of the two streptomycete strains can improve our understanding of the two-component systems of this organism and also provide insight into the molecular mechanisms of regulation in industrially important strains of streptomycetes.

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