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ГЕНЕТИКА

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HOMOLOGUES OF PLEOTROPIC REGULATORY GENE *adpA* IN *ACTINOPLANES*: ANALYSIS *IN SIILICO*

B. Ostash[1], N. Zaburannyi[1,2], L. Horbal[1], A. Luzhetskyy[2], S. Shulga[3], V. Fedorenko[1]

[1]Ivan Franko National University of Lviv
4, Hryshevskyi St., Lviv 79005, Ukraine
e-mail: bohdanostash@gmail.com
[2]Helmholtz Institute for Pharmaceutical Research, Saarland Campus
Building C2.3, 66123 Saarbrucken, Germany
[3]Institute of Food Biotechnology and Genomics of NAS of Ukraine
2a, Osypovskyi St., Kyiv 04123, Ukraine

Actinoplanes teichomyceticus produces glycopeptide antibiotic teicoplanin, a "last line defense" against multidrug resistant cocci. The gene cluster for biosynthesis of teicoplanin (*tcp*) has been cloned 8 years ago, although regulation of its production is poorly understood because of lack of genetic toolkit to manipulate this strain as well as knowledge of its genome organization. In streptomycetes, regulatory gene *adpA* encodes a master regulator of secondary and primary metabolism, as well morphogenesis, forming the largest gene "modulon" known to date for bacteria. Here we analyzed the possibility that AdpA-like protein might be involved in regulation of teicoplanin production. We used the described consensus AdpA operator sequences, inferred from analysis of streptomycete genomes, to screen the *tcp* cluster. Several putative AdpA operators were revealed within *tcp* cluster, implying that AdpA-like transcriptional factors may indeed operate in *Actinoplanes*. Using comparative genomic approaches, we revealed several putative *adpA* homologues in completely sequenced *Actinoplanes* genomes as well as in draft sequence of *A. teichomyceticus* genome. Taken together, our data strongly support the idea that *adpA*-mediated regulation influences the production of antibiotics not only in genus *Streptomyces*, but also in *Actinoplanes*.

Keywords: *Actinoplanes*, teicoplanin, AdpA, genome analysis.

Actinoplanes teichomyceticus is a representative of rare and slow-growing actinomycetes that possess motile spores and produce secondary metabolites not found in more common genera, such as *Streptomyces*, *Micromonospora* or *Saccharopolyspora* [17]. *A. teichomyceticus* is not exception: it is the only known producer of teicoplanin, a clinically valuable glycopeptide active against vancomycin- and methicillin- resistant cocci [1, 5, 6, 14]. *A. teichomyceticus* has also been shown in early works to accumulate second group of antibiotics referred to as teichomycin A_1 complex. It is believed to consist of moenomycin-like antibiotics [1, 3, 12]. Much effort has been put into physiological and genetic studies on teicoplanin biosynthesis [2, 4, 7, 13–16]. There is growing interest in exploration of *A. teichomyceticus*, and *Actinoplanes* in general, as a basis for the development of a new class of antibiotics operating through inhibition of peptidoglycan biosynthesis [11, 12]. In this regard, it is essential to explore all possible ways to stimulate secondary metabolism of actinoplanetes, which will lead to improvement of production of known antibiotics as well as to activation of silent secondary metabolome. Here we decided to explore a possibility that known pleiotropic regulators of secondary metabolism of *Streptomyces* have their counterparts in *Actinoplanes*. Particularly, we focused on gene *adpA* that codes for transcriptional

factor globally affecting the gene expression in several studied model cases [10]. In streptomycetes, AdpA-dependent genes form a largest known to date modulon that is responsible for a number of essential functions as well as production of antibiotics [18]. No information is available about existence of AdpA orthologues in genus *Actinoplanes*, although two completely sequenced genomes of representatives of this genus are available. Here we present *in silico* evidence that AdpA-mediated regulation may operate in *Actinoplanes*, and, in particular, it may be involved in teicoplanin production by *A. teichomyceticus*.

Materials and methods

Genome of *A. teichomyceticus* NRRL-B16726 was sequenced using Illumina approach [9] at company Seq-IT (Germany). Details of sequencing of NRRL-B16726 genome will be reported elsewhere. Complete sequences of *A.* sp. SP50/110 and *A. missouriensis* genomes were retrieved from NCBI website (www. ncbi.nlm.nih.gov/genome). Aminoacid sequences of AdpA orthologous group were downloaded from www.streptomyces.org.uk and NCBI. Programs blast-2seq and CLUSTALW for pairwise (multiple) sequence alignment were accessed at NCBI and www.ebi.ac.uk, respectively [8]. Position-specific weight matrices (PSWM) for AdpA operator sequences were built with the help of programs FIMO and TFBS, and visualized with WebLogo. Orthology of proteins was based on results of reciprocal BLAST results. Phylogenetic analysis of the proteins was carried out on server www.phylogeny.fr. Tree topology was verified with the help of approximate likelihood ratio test (aLRT). In all cases aLRT values were well above minimal threshold of 0.5. PSIPRED was used to analyze protein secondary structure.

Results and discussion

Known *Streptomyces* AdpA operator sequences were retrieved from public sources and used to build PSWM; it is presented as a WebLogo on Fig. 1. The PSWM was used to screen against published sequence of teicoplanin biosynthetic gene (*tcp*) cluster. Indeed, we revealed 3 AdpA-like operators upstream of gene *tcp28* (Fig. 1). The latter encodes putative pathway-specific transcriptional activator of structural genes for teicoplanin biosynthesis. This finding is in accord with currently accepted speculation that global (pleiotropic) regulators of secondary metabolism exert their action via modulation of expression of pathway-specific (cluster-situated) regulatory genes [10].

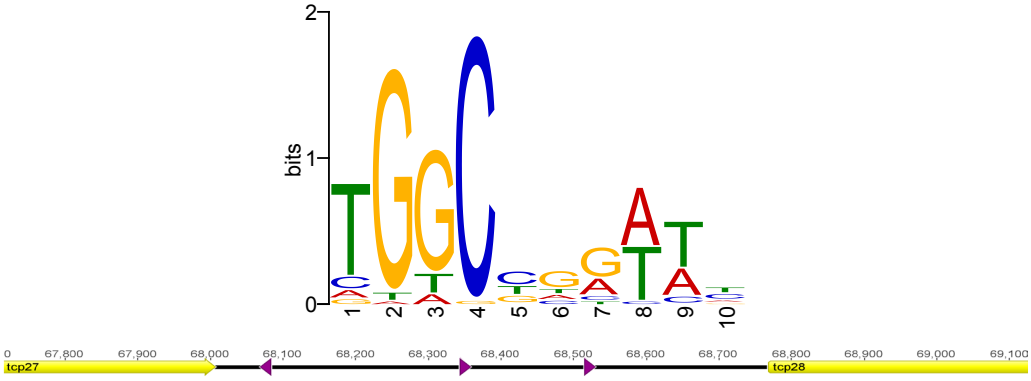

Fig. 1. Consensus AdpA operator sequence presented as WebLogo (top) and location of such sequences (shown as back triangles) within *tcp* cluster upstream of gene *tcp28* (bottom of the figure). Ruler above the genes – distance in base pairs.

Of the three putative AdpA operators within *tcp28* upstream region, one is in orientation opposite to that of *tcp28* transcription. However, since AdpA is known to function as a homodi-

mer, all three AdpA operators could be recognized by AdpA and thus influence *tcp28* expression.

Having discovered that *tcp* cluster contains sequences similar to that of AdpA operators, a question inevitably arises: does *A. teichomyceticus* genome contain orthologue of *Streptomyces* AdpA protein? There is no publicly available genome sequence of *A. teichomyceticus* and focused (PCR-based) approaches towards identification of *adpA* genes are not developed. We therefore set out to partially sequence *A. teichomyceticus* genome and to use it for identification of putative AdpA homologues. The genome of *A. teichomyceticus* was sequenced using reversible terminators approach (Illumina) to approximately 10-fold depth. At this stage, we miss almost 5% of the genome of teicoplanin producer, although the quality is enough to perform an initial screening for AdpA homologues. The genome of *A. teichomyceticus* carries several genes whose translation products resemble AdpA of *Streptomyces griseus* (Fig. 2). The similarity is within 37–49% range, although no synteny was observed. The discovered *A. teichomyceticus* proteins are truncated at the C-termini as compared to streptomycete ones. Analysis of secondary structure of aminoacid sequence of the proteins with the help of PSIPRED and ClustalW revealed typical DNA-binding domain of helix-turn-helix type. Type I glutamine amidotransferase domain was also well represented in these proteins. However, orthology of any of the studied 6 AdpA-like proteins of

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S. coelicolor          MSHDSTAAPEAAARKLSGRRRKEIVAVLLFSGGPIFESSIPLSVFGIDRQDAGV-PRYRLLVCAGEDGPLRTTGGLELT 78
S. ghanaensis          MSHDSTAAPDIAARKLAGRRRKEIVAVLLFSGGPIFESSIPLSVFGVDRQDAGV-PRYRLLVCGGEEGPLRTTGGLELT 78
S. griseus             MSQDS-AAATEAARKLTGRRRREVVAVLLFSGGPIFESSIPLSVFGIDRQDAGV-PRYRLLVCGGEEGPLRTTGGLELT 77
A. teichomyceticus 1   ----------------------MRGHTVAILLLPGASPIDVGIPTQVFAR-RHG----LNYVVVPCAAEIGPVPGRDGLGFH 55
A. teichomyceticus 2   ----------------VRKNRAMPHVIAVLVLDAVVPFDLGVPAQVFGAARHGVARGRPYEVLFCG--EGTVRTAAGFTVT 65
A. teichomyceticus 3   ----------------------MVPRRVALIVDEHSNPFEVGCACEIFGGRRRPQIGYELYELTVVSPTRSVPMRDRLFRVS 60
A. teichomyceticus 4   ----------------------MVTHAVAVLALDRVVPLDLSIPAGIFGEQPDLP-----YRLTVCG-RDPEVATTTGFSIR 55
A. teichomyceticus 5   ----MPYIFKKLPTLRYGGGRMLRSVAVIAMPEVAVFELGVLCELFGYDRTAEGL-PGYDFAVCGVDGGPVPSHSGFTIT 74
A. teichomyceticus 6   ----------------------VSVVVFVLTPQVHLLDLAGPAQVFSTAPGYTLR--------YVAESATVPTWQGVVLH 52
                                              .:  .  .  .  .  .  .  .  .  .  .  .  .  .  .  .  .  .  .

S. coelicolor          APQGLEAISRAGTVVVPAWRS----ITSPPPEEALDALRRAHEEGARIVGLCTGAFVLAAAGLLDGRPATTHWMYAPTL 153
S. ghanaensis          APHGLEAIARAGTVVVPAWRS----ITSPPPQEALDALRRAHEEGARIVGLCTGAFVLAAAGLLDGRPATTHWMYAPTL 153
S. griseus             VEAGLETLDGADTVIVPGFQN----PTGPIDPRVLDALRAAHEEGARIVGLCTGAFVLAAAGLLDGRPATTHWMYAPTL 130
A. teichomyceticus 1   VEAGLETLDGADTVIVPGFQN----PTGPIDPRVLDALRAAAFRGARMVSICGGAFALAAAGILDGRRATTHWLNAGRL 130
A. teichomyceticus 2   PDHPLSAAERADTVLVPGINAGGPVTDGTLPEPVRAALHSAADRGARIVSICTGASVLAAAGLLDGRPAATHWGWAKRI 142
A. teichomyceticus 3   APGRLSDLDRADMIIVPNRPD----VDVPSRGAVLAAIRRAHARGARLVGLCTGAFTLAEAGVLDGRRAAVHWQLAPDF 135
A. teichomyceticus 4   VPGTLDDARRADTLIVPGYTG----AGGDLPDQVLDTITQVHARGGRVVSICSGAFALAAAGLLDGRRATTHWSRAAEL 129
A. teichomyceticus 5   PSHDLAPAWTADLVAVVPNDVR------QAPAEVLDVLRHAHDRGAWVMSVCTGAFTLGEAGLLDDRRCTTHWRYTDSL 147
A. teichomyceticus 6   ADLEWPALTPDDLVVVPGWSAG----HGFFRTGTLRRIADHHAAGGTVASVCAGADALGRAGLLDGRRCTTHHDLQDLL 125
                                .  *  .  .  .  .  .  .  .  .  .  .  .  .  .  .  .  .  .  .  .  .  .  .

S. coelicolor          AKRYPSVHVDPRELFVDDGDVLTSAGTAAGIDLCLHIVRTDHGNEAAGALARRLVVPPRRSGGQERYLDRSLPEEIGAD 232
S. ghanaensis          AKRYPSVHVDPRELFVDDGDVLTSAGTAAGIDLCLHIVRTDHGHEAAGALARRLVVPPRRSGGQERYLDRSLPEEIGAD 232
S. griseus             AKRYPSVHVDPRELFVDDGDVLTSAGTAAGIDLCLHIVRTDHGTEAAGALARRLVVPPRRSGGQERYLDRSLPEEIGSD 231
A. teichomyceticus 1   AREYPKVRVDDSVLFVDDGQVLTAAGVAAGIDLCLHIVRRDHGVQASNEIARVMVAAPYRSGGQAQYVPRSIPEPLG-D 209
A. teichomyceticus 2   GGLYPRVRWDFDVLFMDDGDVLTSAGVGAGVDLCLHIVRSDYGAEVANAAARRCVVPPWRDGGQAQYIERPVPPAAG-S 221
A. teichomyceticus 3   HRRFPAVRLEPDVLFVDDGDILTSAGSAAALDLGLHIVRRDHGTEVANRVGRQLVFAAFRDGGQRQFVERPLPAPAT-S 214
A. teichomyceticus 4   ARRYPRITVDPHVLYVDEGQLLTSAGVSAGIDLCLYLVRRDHGAAAANRVARNVVAAPHRDGGQAQFIASPVAADDD-A 208
A. teichomyceticus 5   AARFPRAKVDPGVLYVVDGTVLTSAGTAAAIDCGLHLIREEQGSAVAAQIARRMVVPPHRDGGQAQFIETPIPTMASCA 226
A. teichomyceticus 6   ARSYPRSSVIRDVLYVSDDRVVTSAGIASGIDLALHLVALRHGPAVAARVAREMVVYARRNGDEQQAGVMLRHRAHLSD 204
                          :*       *:: :. ::*:** .:.:*  *:::    *  .:   .*  *  . *.*:: :

S. coelicolor          AKRYPSVHVDPRELFVDDGDVLTSAGTAAGIDLCLHIVRTDHGNEAAGALARRLVVPPRRSGGQERYLDRSLPEEIGAD 232
S. ghanaensis          AKRYPSVHVDPRELFVDDGDVLTSAGTAAGIDLCLHIVRTDHGHEAAGALARRLVVPPRRSGGQERYLDRSLPEEIGAD 232
S. griseus             AKRYPSVHVDPRELFVDDGDVLTSAGTAAGIDLCLHIVRTDHGTEAAGALARRLVVPPRRSGGQERYLDRSLPEEIGSD 231
A. teichomyceticus 1   AREYPKVRVDDSVLFVDDGQVLTAAGVAAGIDLCLHIVRRDHGVQASNEIARVMVAAPYRSGGQAQYVPRSIPEPLG-D 209
A. teichomyceticus 2   GGLYPRVRWDFDVLFMDDGDVLTSAGVGAGVDLCLHIVRSDYGAEVANAAARRCVVPPWRDGGQAQYIERPVPPAAG-S 221
A. teichomyceticus 3   HRRFPAVRLEPDVLFVDDGDILTSAGSAAALDLGLHIVRRDHGTEVANRVGRQLVFAAFRDGGQRQFVERPLPAPAT-S 214
A. teichomyceticus 4   ARRYPRITVDPHVLYVDEGQLLTSAGVSAGIDLCLYLVRRDHGAAAANRVARNVVAAPHRDGGQAQFIASPVAADDD-A 208
A. teichomyceticus 5   AARFPRAKVDPGVLYVVDGTVLTSAGTAAAIDCGLHLIREEQGSAVAAQIARRMVVPPHRDGGQAQFIETPIPTMASCA 226
A. teichomyceticus 6   ARSYPRSSVIRDVLYVSDDRVVTSAGIASGIDLALHLVALRHGPAVAARVAREMVVYARRNGDEQQAGVMLRHRAHLSD 204
                          :*       *:: :. ::*:** .:.:*  *:::    *  .:   .*  *  . *.*:: :

S. coelicolor          PLAEVVAWALEHLHEQFDVETLAARAYMSRRTFDRRFRSLTGSAPLQWLITQRVLQAQRLLETSDYSVDEVAGRCGFRS 311
S. ghanaensis          PLAEVVAWALEHLHEQFDVETLAARAYMSRRTFDRRFRSLTGSAPLQWLITQRVLQAQRLLETSDYSVDEVAGRCGFRS 311
S. griseus             PLAEVVAWALEHLHEQFDVETLAARAYMSRRTFDRRFRSLTGSAPLQWLITQRVLQAQRLLETSDYSVDEVAGRCGFRS 310
A. teichomyceticus 1   VFALTREWALAHLEQPLTVAVLARHAGVSARTFGRRFVEDTGYTPMQWVLRARVDLARELLERTDLGVDQIAARVGVGT 287
A. teichomyceticus 2   GTEPTRAWVLDRLSEPVTLEEMARHARMSVRTFTRRFRDETGSSPRQWLLRQRVEHARLLLESTDLAVDVVARRSGLGS 299
A. teichomyceticus 3   PLAPVLQWAQERLHLRLSVDDLARHGRMSTATLHRRFRNEVGSTPLAWLTAQRVALACRLIEQGAAGVDAVARQSGLGT 292
A. teichomyceticus 4   ALSGVRAWALAHLDRPVSVPELARHAAMAPRTFARRFVAETGHTPLQWLLHARIDRARELLESSTLSIGQIADSTGLGS 286
A. teichomyceticus 5   TLQPLLAHLLETLDREHTVETMADAVHMAARTFARRFRAETGATPHDWLTGQRVLLARRLLEETDLSVEAIAGRAGFGS 305
A. teichomyceticus 6   VVHRVQDRIDASFDGPLRLAGLAAGAGVSERTLLTRLFTAATGRTPLQYQQLLRVERAEYLIGHG-STVEAAARAVGFGD 283
                          :  .  .  .  .  .  .  .  .  .  .  .  .  .  .  .  .  .  .  .  .  .  .  .  .  .

S. coelicolor          PVALRGHFRRQLGSSPAAYRAAYRARRPQGDRQPDPD-TAAAG-------ATRPLPPSDP--PASLAPENAVPFQTRRT 388
S. ghanaensis          PVALRGHFRRQLGSSPAAYRAAYRARRPQADRNQDTDGTANAPGGVPSGQQGHPGLPGHPGQSAALHPEQPLPHQSRRT 390
S. griseus             PVALRGHFRRQLGSSPAAYRAAYRARRPQG--VAESAATVVET------MVPSQGPPSGR-RGSTLSSAAVAVAASVGS 386
A. teichomyceticus 1   GANLRMHFQRILRISPSEYRRTFAAAPGGGP-----------------------------------KLAEAGAAASARRS 353
A. teichomyceticus 2   AAALRQHLHATIGVAPSAYRRTFRHAG---------------------------------------------------- 361
A. teichomyceticus 3   AANLRALLRKHVGLSPSEYRRRFAADGAR---------------------------------------------------- 356
A. teichomyceticus 4   AINLRVHFRNLVGTTPSAYRRAFRTTADVS---------------------------------------------------- 349
A. teichomyceticus 5   AQTLRHHFTQRLSTTPQAYRSTFKAKV------------------------------------------------------ 367
A. teichomyceticus 6   ARMLR-RLRSRAATLPA---------------------------------------------------------------- 333
                          **  :  *

S. coelicolor          ATPMPAG----------------------AASVPGQRSAP 398
S. ghanaensis          AAASSLGPSLTASASPADSGREAYVPTRAGVPGQRSAP 428
S. griseus             GELSLPGP-------------DAYVPGRPALPGQRSAP 405
A. teichomyceticus 1   GAAAR---------------------------------- 337
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Fig. 2. Multiple sequence alignment of known AdpAs and *A. teichomyceticus* homologues (1-6). Rectangle marks DNA binding domain.

A. teichomyceticus to known AdpA proteins from either *S. coelicolor* or *S. griseus* could not be readily established in a series of reciprocal BLAST searches. No synteny was observed between *adpA* loci of streptomycetes and that of *A. teichomyceticus*. This is probably because *Streptomyces* and *Actinoplanes* are only remotely related actinomycete genera.

We explored alternative ways to establish relatedness of *A. teichomyceticus* sequences to known AdpA proteins. It is possible that AdpA sequences of *S. coelicolor* and *S. griseus* are not optimal ones to screen *Actinoplanes* genome for AdpA orthologues. Phylogenetic tree of *Streptomyces* AdpA proteins is very coherent, yet it did form several distinct clades and branches clearly divergent from SGR_4742 and SCO_2792 (AdpA proteins from *S. griseus* and *S. coelicolor*, respectively; data not shown). AdpA protein from *S. clavuligerus* (SCLAV_1957) is located in such divergent clade, and function of this protein has been experimentally verified. Reciprocal BLASTP searches confirmed that completely sequenced genomes of *A. missouriensis* and *A. sp*. SE50/110 contained proteins AMIS_10050 and ACPL_1231, respectively, orthologous to SCLAV_1957. The orthology of both *Actinoplanes* proteins to the other members of *Streptomyces* AdpA group cannot be inferred from BLAST searches, suggesting unequal value of AdpA from different species origin for interrogation of remotely related genomes. Nevertheless, an ability to find *Actinoplanes* orthologs to certain AdpA sequences implies that non-*Streptomyces* AdpA proteins might indeed exist. Additional searches turned up more AdpA orthologues from two other genomes of the family *Micromonosporaceae*, a home to genus *Actinoplanes*: SACE_4523 (*Saccharopolyspora erythraea*) and Micau_1999 (*Micromonospora aurantiaca*). A resulting tree of the aforementioned proteins is shown on Fig. 3.

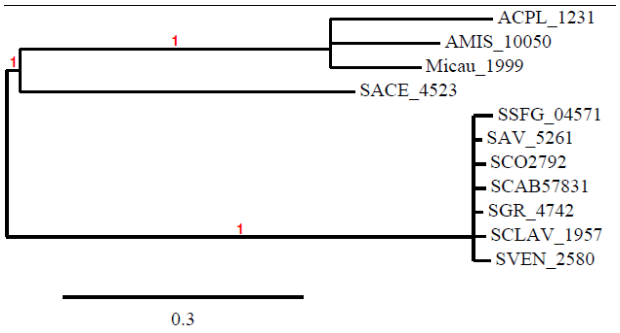

Fig. 3. Maximum-likelihood tree of *Streptomyces* AdpA proteins and putative AdpA from selected *Micromonosporaceae* genomes. Branches with aLRT values (numbers at nodes) less that 0.8 were collapsed. Protein abbreviations – see the text. The scale bar under the tree indicates number of aa substitution per aa position.

Proteins Micau_1999 and AMIS10050 were subjected to pairwise blast2seq alignment with six AdpA-like sequences found in *A. teichomyceticus* genome (At-1 to At-6, see also Fig. 2). The results of these analyses are summarized in Table 1. Of the six proteins compared, At-2 and At-5 displayed the highest similarity to both AMIS_10050 and ACPL_1231. Respective expectation (e) values were close for both At-proteins, making it challenging to determine the best *A. teichomyceticus* hit to AMIS_10050 and ACPL_1231. Reciprocal BLAST with the respective genomes confirmed that only At-2 protein is orthologous to AMIS_10050, although the former failed to show orthology to ACPL_1231. Thus, while, *Streptomyces* AdpA sequences behave as typical cluster of orthologous proteins, the AMIS_10050, ACPL_1231 and At-proteins do not show the same robust behavior, irrespective of the type and parameters of BLAST search being employed.

Table 1

Results of BLASTP comparison of AMIS10050 and ACPL_1231 to *A. teichomyceticus* homologues

***A.t.* protein**		**comparison to AMIS_10050**			**comparison to ACPL_1231**		
Name[1]	Size, aa	ID/SI[2], %	e-value[3]	Gaps	SI/ID, %	e-value	Gaps
At-1	327	43/59	$3e^{-77}$	10/317	44/60	$2e^{-81}$	10/316
At-2	333	45/59	$3e^{-85}$	4/313	44/59	$7e^{-83}$	12/316
At-3	322	44/58	$3e^{-80}$	8/319	43/58	$5e^{-77}$	12/323
At-4	317	46/62	$6e^{-72}$	6/314	47/62	$8e^{-73}$	6/318
At-5	338	47/62	$7e^{-85}$	5/314	46/62	$2e^{-85}$	5/318
At-6	298	35/48	$2e^{-35}$	2/262	36/48	$5e^{-35}$	2/262

Comments. [1]As mentioned in Fig. 2

[2]Percentage of identity and similarity

[3]The lowest e-values, showing the most significant similarity, are highlighted in grey

Our work is the first attempt to identify in *Actinoplanes* a functional counterpart of *Streptomyces* pleiotropic regulator AdpA. Here we provide initial bioinformatic evidence that *tcp* cluster of *A. teichomyceticus* contains putative operator sequences for Adp family proteins. We partially sequenced *A. teichomyceticus* genome and identified a set of genes encoding AdpA homologues. Comparative genomic analyses of the other completely sequenced *Actinoplanes* genomes revealed proteins showing orthology to certain *Streptomyces* AdpA proteins. These *A. missouriensis* and *A. sp.* SE50/110 orthologs of AdpA allowed us to narrow down the list of 6 *A. teichomyceticus* AdpA-like protein to two candidates for the role of true AdpA protein. It should be noted that, unlike in *Streptomyces*, the *Actinoplanes* AdpA-like sequences under study diverged from *Streptomyces* AdpA significantly enough to prevent any reliable prediction of AdpA orthologs for the entire genus *Actinoplanes* from the results of BLAST or synteny only. Despite these challenges, our data suggest that AdpA-like regulation may operate in *Actinoplanes*, and we currently are pursuing experimental verification of the identified AdpA homologues from *A. teichomyceticus.*

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ГОМОЛОГИ ПЛЕЙОТРОПНОГО РЕГУЛЯТОРНОГО ГЕНА *adpA* В *ACTINOPLANES*: АНАЛІЗ *IN SIILICO*

Б. Осташ[1], Н. Забуранний[1,2], Л. Горбаль[1], А. Лужецький[2], С. Шульга[3], В. Федоренко[1]

[1]Львівський національний університет імені Івана Франка
вул. Грушевського, 4, Львів 79005, Україна
e-mail: bohdanostash@gmail.com
[2]Гельмгольц-інститут фармацевтичних досліджень Саарланду,
Саарланд-кампус
буд. С2.3, Саарбрюкен 66123, Німеччина
[3]Інститут харчової біотехнології та геноміки НАНУ
вул. Осиповського, 2а, Київ 04123, Україна

Actinoplanes teichomyceticus продукує глікопептидний антибіотик тейкопланін, що є антибіотиком "останньої лінії оборони" проти мультирезистентних коків. Кластер генів біосинтезу тейкопланіну (*tcp*) клоновано 8 років тому, хоча регуляція продукції цього антибіотика погано зрозуміла внаслідок браку розроблених методів

генетичних маніпуляцій цим видом, а також відсутності даних про будову генома *A. teichomyceticus*. У стрептоміцетів регуляторний ген *adpA* кодує один із ключових регуляторів вторинного та первинного метаболізму, а також морфогенезу, формуючи найбільший на сьогодні генний "модулон", що описано у бактерій. Ми проаналізували гіпотезу про те, що AdpA-подібний білок може бути задіяно у регуляції продукції тейкопланіну. Використовуючи описану консенсусну операторну послідовність AdpA для стрептоміцетів, ми здійснили пошук відповідних операторів у *tcp*-кластері. Виявлено кілька імовірних операторів AdpA, що вказує на те, що AdpA-залежна регуляція може функціонувати в *Actinoplanes*. З використанням низки методів порівняльної геноміки виявлено кілька гомологів *adpA* у повністю просеквенованих геномах *Actinoplanes*, а також у чорновій послідовності генома *A. teichomyceticus*. У сумі наші дані узгоджуються з припущенням, що *adpA*-залежна регуляція впливає на продукцію антибіотиків не тільки в роді *Streptomyces*, але й у роді *Actinoplanes*.

Ключові слова: *Actinoplanes*, тейкопланін, AdpA, геномний аналіз.

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Б. Осташ[1], Н. Забуранный[1,2], Л. Горбаль[1], А. Лужецкий[2], С. Шульга[3], В. Федоренко[1]

[1]Львовский национальный университет имени Ивана Франко
ул. Грушевского, 4, Львов 79005, Украина
e-mail: bohdanostash@gmail.com
[2]Гельмгольц-институт фармацевтических исследований Саарланда, Саарланд-кампус
д. С2.3, Саарбрюкен 66123, Германия
[3]Институт пищевой биотехнологии и геномики НАНУ
ул. Осыповского, 2а, Киев 04123, Украина

Actinoplanes teichomyceticus продуцирует гликопептидный антибиотик тейкопланин, который является антибиотиком "последней линии обороны" против мультирезистентных кокков. Кластер генов биосинтеза тейкопланина (*tcp*) клонирован 8 лет назад, однако регуляция продукции тейкопланина слабо изучена из-за почти полного отсутствия методов генетических манипуляций этим видом, а также отсутствия данных о строении генома *A. teichomyceticus*. У стрептомицетов регуляторный ген *adpA* кодирует один из ключевых регуляторов вторичного и первичного метаболизма, а также морфогенеза, формируя самый большой среди известных сегодня бактериальных генных "модулонов". Мы проанализировали гипотезу о том, что AdpA-подобный белок может участвовать в регуляции продукции тейкопланина. Используя описанную консенсусную операторную последовательность AdpA в стрептомицетах, мы выполнили поиск соответствующих операторов в пределах *tcp*-кластера. Выявлены несколько вероятных операторов AdpA, что указывает на вероятность AdpA-зависимой регуляции в *Actinoplanes*. С использованием ряда методов сравнительной геномики выявлены несколько гомологов *adpA* в полностью просеквенированных геномах *Actinoplanes*, а также в черновой последовательности генома *A. teichomyceticus*. В сумме наши данные согласуются с предположением, что *adpA*-зависимая регуляция влияет на продукцию антибиотиков не только в роде *Streptomyces*, но и в роде *Actinoplanes*.

Ключевые слова: *Actinoplanes*, тейкопланин, AdpA, геномный анализ.