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MOLECULAR BIOLOGY

# Diversity of Polyketide Synthase Genes in the Genomes of Heterotrophic Microorganisms Isolated from Epilithic Biofilms of Lake Baikal

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**Abstract**—Many bacterial secondary metabolites, including pharmacologically promising compounds, are synthesized by polyketide synthases (PKS) enzyme complexes. In the present work, nucleotide sequences of the genes encoding 16S rRNA and PKS of heterotrophic bacterial strains isolated from epilithic biofilms of the littoral zone of Lake Baikal were determined. On the basis of molecular phylogenetic analysis of the 16S rRNA genes, six heterotrophic strains were identified: *Serratia fonticola* 1A and 10A, *Pseudomonas umsongensis* K10-2 and K10-3, *Rheinheimera tilapiae* K18, and *Flavobacterium* sp. 43-09. Sequencing of cloned amplification products for PKS gene cluster revealed 33 sequences. Genes involved in biosynthesis of antibiotics (difficidine, erythromycin, curacin, mixalamide, corallopyronin, and myxothiazol) and cytostatics (romidepsin, spiruchostatin, and disorazol) were found among homologous sequences. The low homology (50–83%) of the PKS amino acid sequences of Baikal bacteria with sequences from GenBank attests to the potential capability of strains to produce new, not yet studied bioactive compounds. The obtained results show that the studied strains may be of practical interest for biotechnological application.

*Keywords:* polyketide synthase genes, 16S rRNA, heterotrophic microorganisms, Lake Baikal, cloning, epilithic biofilms.

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## INTRODUCTION

Lake Baikal is the largest and the deepest freshwater reservoir on Earth and is characterized by great biodiversity and a high degree of endemism of aquatic organisms, unique environmental features, and richness of biotopes being a kind of natural laboratory for studying the metabolic potential of microbial communities. It is known that microorganisms produce a huge number of biologically active substances (BAS), many of which are used in biology and medicine. It was shown that the microbial communities inhabiting unique and extreme habitats are the most important resource of new and rare metabolites [1–3]. Recently, special attention in the search for new biologically active substances has been paid to the microbial communities of biofilms, since it is known that 95–99% of microorganisms in natural conditions exist in the form of specifically organized microbial associations attached to the substrates [4]. Biofilms formed on the rocks (epilithic) are, as a rule, morphologically and physiologically heterogeneous structures with rich species composition and high number of bacteria that have a diversity of metabolic pathways and form a complex system of cooperative and competitive interactions [5]. It is obvious that the search for producers of various biologically active substances in the microbial communities of biofilms is promising.

To date, it has been shown that a wide range of secondary metabolites of bacterial origin is synthesized by multidomain enzymes megasynthases: polyketide synthase (PKS), nonribosomal peptide synthetase (NRPS), and their hybrid complexes PKS/NRPS [6].

Polyketides are characterized by diverse chemical structure and functional activity, including antibiotics, statins, inhibitors of tumors, and many other pharmaceutically important compounds. Three types of PKS (I, II, and III) differing in the structure and mechanism of catalysis are known. PKS type I is organized in modules consisting of at least three domains: ketoacyl-synthase (KS), acyltransferase (AT), and acyl-carrying protein (ACP). Each module is responsible for one cycle of elongation of the polyketide chain [6]. Primers specific to the conservative regions of the KS-domain of PKS are successfully used for detection and identification of the genes responsible for the synthesis of secondary metabolites of a polyketides nature in the bacterial genomes [1, 3, 7]. For example, this approach was applied to study the microorganisms

† Deceased.

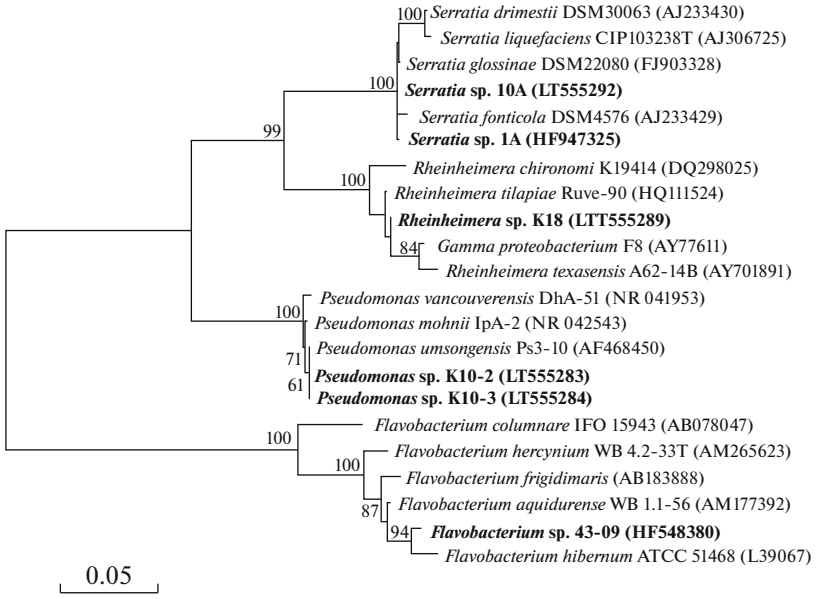


**Fig. 1.** Phylogenetic tree on the basis of comparison of 16S rRNA gene fragments with a length of 1429 bp of the genera *Serratia*, *Pseudomonas*, *Rheinheimera*, and *Flavobacterium*. Sequences obtained in this study are indicated by boldface.

associated with the aquatic organisms of Lake Baikal [9, 10]. The authors showed that, in the metagenomic community of the Baikal endemic sponges *Lubomirskia baicalensis* and *Swartschewskia papyracea*, there are sequences of the genes encoding the biosynthesis of curacin A, stigmatellin, and nostophycin [8, 9]. The PKS and NRPS genes were identified in the genomes of 9 of 14 cultures of the genera *Bacillus*, *Pseudomonas*, *Variovorax*, *Curtobacterium*, and *Rhodococcus* isolated from *L. baicalensis* [10].

The goal of the present work is to assess the diversity of the genes of polyketide synthases in the genomes of heterotrophic bacteria isolated epilithic biofilms of Lake Baikal.

## MATERIALS AND METHODS

Six strains of heterotrophic bacteria from the collection of the laboratory of aquatic microbiology of the Limnological Institute (Siberian Branch, Russian Academy of Sciences) isolated from epilithic of biofilms were studied. Biofilms were sampled in the littoral zone of Lake Baikal near Listvyanka settlement and in Maloe More strait in 2012. Strains were previously identified as the representatives of the genera *Rheinheimera*, *Pseudomonas*, *Serratia* (Proteobacteria), and *Flavobacterium* (Bacteroidetes) by morphological, physiological, and biochemical characteristics and on the basis of the sequences of the 16S rRNA genes.

Sequence alignment of the 16S rRNA genes (length 1429 bp) and construction of a phylogenetic tree was made with the Mega 6.06 software package using the maximum likelihood method (Kimura's two parameter model). Bootstrap support was calculated for 1000 replicas.

For search and identification of PKS genes, DNA was extracted from 100 μL of the daily culture suspension according to the protocols of the manufacturer with DNA-sorb B (Rospotrebnadzor, Russia). Amplification of fragments of the KS-domain of the PKS genes was performed using degenerate primers DK-F (5'-GTGCCGGTNCCRTGNGYYTC-3') and DK-R (5'-GCGATGGAYCCNCARCARYG-3') as described previously [8]. Amplicon was visualized in 1% agarose gel using transilluminator (VL-6.MC, France). PCR fragments were cloned in the vector pJET1.2/blunt (CloneJET PCR Cloning Kit, Fermentes, Lithuania) and then the transformation of the competent cells of *E. coli* DH-5α was conducted.

The nucleotide sequences were determined on a 3500xL genetic analyzer (Applied Biosystems, United States). Comparative analysis of the obtained sequences was performed using the BLASTX and BLASTP software packages.

The nucleotide sequences of the PKS gene fragments (33 pieces) were deposited in GenBank under the numbers: LT220194–LT220203, LT555230–LT555239, LT555293–LT555305.

## RESULTS AND DISCUSSION

*Phylogenetic Analysis of 16S rRNA Genes.* BLAST analysis of nucleotide sequences of the 16S rDNA of *Serratia* spp. 1A and 10A from Lake Baikal showed 99.8% similarity to typical strains of *Serratia fonticola* DSM 4576 and *Serratia glossinae* DSM 22080T. The sequence of the 16S rRNA gene of the Baikal isolates and these strains formed a joint cluster on the tree (Fig. 1). Bacterium *S. glossinae* was isolated in 2010

from the gut of tsetse fly (*Glossina palpalis gambiensis*), which is known as a carrier of trypanosomes—the causative agents of sleeping sickness in African countries [11]—and *S. fonticola* was isolated from drinking water in 1979 [12]. Later, by the results of physiological and biochemical tests and DNA hybridization, it was established that *S. fonticola* and *S. glossinae* have no significant differences and, therefore, are synonymous species [13]. Thus, taking into account our results and literature data, the Baikal strains of *Serratia* spp. 1A and 10A have been attributed to the *S. fonticola* species.

BLAST analysis of the 16S rRNA gene sequences of the K10-2 and K10-3 strains of *Pseudomonas* spp. revealed their identity (100%) with a typical species of *Pseudomonas umsongensis* Ps3-10 isolated from acidic agricultural soils in Korea. When cultivated, the species had the ability to recover nitrates and grow at 4°C [14]. On the phylogenetic tree of 16S rRNA gene sequences of *Pseudomonas* strains from Lake Baikal and *P. umsongensis* Ps3-10 were grouped into one cluster (Fig. 1).

When comparing the nucleotide sequence of the 16S rDNA of *Rheinheimera* sp. K18 with the sequences from the data bank, we identified a high similarity (99.3%) with *Rheinheimera tilapiae* Ruye-90 isolated from the tilapia intestine (*Tilapia rendalli*) cultivated in a pond in Taiwan [15]. The sequence of the 16S rRNA gene of the K18 strain of *Rheinheimera* sp. formed a sister branch on the tree with *R. tilapiae* Ruye-90 (Fig. 1). *Rheinheimera* sp. K18 was preassigned to the *R. tilapiae* species.

The sequence of the 16S rRNA gene of the *Flavobacterium* sp. 43-09 strain from epilithic biofilms of Lake Baikal formed a sister branch with the Antarctic *Flavobacterium hibernum* ATCC 51468 (Fig. 1) [16]. The similarity of the 16S rRNA genes of the Baikal isolate and *F. hibernum* was 98 and 99.9% with *Flavobacterium* sp. JRM isolated from the ice cover of the Susquehanna River in the United States. According to the recent whole genome sequencing data, the latter was named *Flavobacterium falloni*. Our isolated strain *Flavobacterium* sp. 43-09 obviously belongs to the same species.

*Identification of the PKS Genes.* For the studied six strains of heterotrophic bacteria from Lake Baikal, 33 nucleotide sequence of the PKS genes were identified, which were 72–100% similar to the homologous sequences from the database GenBank. The closest amino acid sequences identified by BLASTP analysis are presented in Table 1, and identified PKS are shown in Table 2.

For the 1A and 10A strains of *S. fonticola*, 12 and 8 PKS gene sequences, respectively, were identified. The greatest similarity (72–96%) of the selected nucleotide sequences is observed with the genes of bacteria of the genera *Burkholderia*, *Chromobacterium*, *Enterobacter*, and *Paenibacillus* (Table 1). Among related sequences, genes encoding the synthesis of antibiotics (erythromycin and difficidin) and antitumor agents (romidepsin, spiruchostatin, and disorazol) were identified. The percentage of sequence homology of the PKS genes of *S. fonticola* with known enzymes was relatively low (50–83%) (Table 2). Previously, for *S. fonticola* 1A, the presence of antagonistic activity against four opportunistic pathogens (*Escherichia coli* M17-02, *Bacillus subtilis* ВКПМ, *Staphylococcus aureus* ATCC 25923, *Enterococcus faecium)* was demonstrated [17].

Eighteen sequences of the PKS genes of the strains 1A and 10A *S. fonticola* at 80–83% are similar to the genes for the synthesis of cytostatic romidepsin (DepB and DepC). Romidepsin is a bicyclic depsipeptide isolated in 1994 in Japan from a soil bacterium *Chromobacterium violaceum*. This compound is produced by the Celgene firm as an antitumor drug Istodax for the treatment of T-cell lymphomas and other peripheral T-cell lymphomas. Romidepsin inhibits the activity of the enzyme histone deacetylase and, thus, induces apoptosis of lymphocytes. According to recent studies, romidepsin can be used for reactivation of latent human immunodeficiency virus with the goal of depleting its population [18].

Some species of *Serratia*, such as *S. plymuthica*, *S. rubidaea*, *S. marcescens*, and *S. nematodiphila*, form a red pigment prodigiosin, an alkaloid compound with antimicrobial, antimalarial, antitumor, and immunodepressive properties [19]. In addition, strains of the *Serratia* genus produce other useful secondary metabolites, including oocydin A, carbapenem, althiomycine, bacteriocins, and serrawettin [19]. Serrawettins are biodegradable nonionic surfactants extremely in demand in the industry. New soil *Serratia surfactantfaciens* sp. produces both prodigiosin and serrawettin, has antimicrobial activity, inhibits the development of tumors, and is useful for bioremediation [19].

In the genomes of the *P. umsongensis* K10-2 and K10-3, two and three PKS gene sequences, respectively, were identified (Table 1). Among the closest homologues (99–100%), PKS type I (ACN67520) from *Pseudomonas putida* was identified and KS-domain clusters of the erythromycin biosynthesis from *Burkholderia* sp. BT03 with a homology of 61% (Table 2). The studied strains of the genus *Pseudomonas* can be potentially capable of synthesis of new biologically active substances, since bacteria of this genus produce 795 secondary metabolites, including 610 antibiotics and 185 substances with a broad spectrum of activity [19]. Among the produced compounds are mupirocin, pyroles, phloroglucinol, phenazine, benzaldehyde, quinoline, quinolone, phenanthren, phthalate, andrimid, moiramides, zafrin, and bushrin [20, 21]. In the Baikal strain of *P. fluorescens* 28Bb-06 isolated from a sponge, PKS genes 50–66% similar to the genes of the biosynthesis of

**Table 1.** Closest homologs for sequences of the PKS genes from microorganisms of Lake Baikal

| Strain | No. of clone | Results of BLASTP analysis | |
|---|---|---|---|
| | | Closest homologs | Homology, % |
| *Serratia fonticola* 1A and 10A | 1A-1; 1A-3; 1A-7; 1A-10; 1A-11; 1A-12; 1A-13 10A-6; 10A-7 | Polyketide synthase *Burkholderia* sp. TSV86 (WP_059568895) | 80–81 |
| | 1A-2 | Polyketide synthase *Burkholderia thailandensis* (WP_043296479) | 82 |
| | 1A-4; 1A-6; 1A-9 | Polyketide synthase *Burkholderia thailandensis* E264 (ABC38737) | 85 |
| | 1A-5 | Polyketide synthase *Enterobacter cloacae* (WP_063925842) | 96 |
| | 10A-1; 10A-2; 10A-4; 10A-5; 10A-8 | Polyketide synthase *Burkholderia thailandensis* (WP_059844334) | 84–85 |
| | 10A-3 | Polyketide synthase *Paenibacillus* sp. F6-B70 (ACT85958)<br>Polyketide synthase *Paenibacillus polymyxa* (KJD37325) | 73<br>72 |
| *Pseudomonas umsongensis* K10-2 and K10-3 | K10-2-1; K10-2-2; K10-3-1; K10-3-2; K10-3-6 | Polyketide synthase *Pseudomonas putida* (ACN67520) | 99–100 |
| *Rheinheimera tilapiae* K18 | 18-1; 18-2 | Polyketide synthase *Rheinheimera* sp. F8 (ALZ75986) | 93–94 |
| | 18-3; 18-6 | Polyketide synthase *Rheinheimera* sp. F8 (ALZ75984) | 95 |
| | 18-4; 18-5 | Eritronolide synthase B Candidatus *Accumulibacter* sp. BA-92 (EXI82404)<br>Polyketide synthase *Achromobacter* sp. RTa (WP_043548713) | 78<br>78 |
| *Flavobacterium* sp. 43-09 | 43-9; 43-15 | Polyketide synthase *Flavobacterium* sp. JRM (WP_039119622) | 97–99 |

yersiniabactin, rhizoxin, disorazol, and epothilone were discovered [22].

For the K18 strain *R. tilapiae*, six amino acid sequences of PKS were predicted. Among the closest homologues (93–95%), the PKS genes that belong to the *Rheinheimera* sp. F8 were found, and their sequences were determined by whole genome sequencing (Table 1). The formation of stable filaments of extracellular DNA is a feature of the strain *Rheinheimer*a sp. F8 isolated from the biofilms of the Saskatchewan River (Canada) [23]. Among sequences related to the Baikal strain (homology 58–78%), the PKS genes synthesizing antibiotics (erythromycin, myxalamid, curacin, and myxothiazol) were detected (Table 2). Currently, metabolites synthesized by the PKS in the bacteria of the *Rheinheimera* genus were not revealed.

**Table 2.** Homologues with identified enzymes closely related to the Baikal sequences of PKS

| Strain | No. of clone | Results of BLASTP analysis | |
|---|---|---|---|
| | | Homologues with identified PKS | Homology, % |
| *Serratia fonticola* 1A and 10A | 1A-1, 1A-3, 1A-7, 1A-10, 1A-11 1A-12, 1A-13; 10A-6, 10A-7 | Romidepsin synthase DepC *Chromobacterium violaceum* 968 (ABP57747); | 80 |
| | | Spiruchostatin synthase SpiC1 *Pseudomonas* sp. Q71576 | 78 |
| | 1A-2, 1A-4, 1A-6, 1A-9; 10A-1, 10A-2, 10A-4, 10A-5, 10A-8 | Romidepsin synthase DepB *Chromobacterium violaceum* 968 (ABP57746) | 83 |
| | 1A-5 | Disorazol synthase DszA *Sorangium cellulosum* So ce12c (AAY32964) | 50 |
| | 10A-3 | Eritronolide synthase B *Dickeya* sp. NCPPB 3274 (WP_042861990) | 70 |
| | | Difficidine synthase DfnD *Bacillus* sp. 916 (EJD67453) | 66 |
| *Pseudomonas umsongensis* K10-2 and K10-3 | K10-2-1; K10-2-2; K10-3-1; K10-3-2; K10-3-6 | Eritronolide synthase B *Burkholderia* sp. BT03 (WP_024163149) | 61 |
| *Rheinheimera tilapiae* K18 | K18-1, K18-2 | Eritronolide synthase B *Methylobacter tundripaludum* SV96 (WP_006892897) | 66 |
| | | Mixalamide synthase MxaE *Stigmatella aurantiaca* (AAK57189) | 64 |
| | K18-3, K18-6 | Myxothiazol synthase MtaB *Stigmatella aurantiaca* DW4/3-1 (AAF19810) | 59 |
| | | Curacin synthase, CurL *Lyngbya majuscula* 19L (AAT70107) | 58 |
| | K18-4, K18-5 | Eritronolide synthase B *Accumulibacter* sp. BA-92 (EXI82404) | 78 |
| *Flavobacterium* sp. 43-09 | 43-09-9; 43-09-15 | Disorazol synthase DszA *Sorangium cellulosum* So ce12c (AAY32964) | 57 |
| | | Corallopyronin synthase CorB *Corallococcus coralloides* B035 (ADI59532) | 56 |

Two sequences of the PKS gene identified in the genome of the *Flavobacterium* sp. 43-09 have a high degree of homology (97–99%) with the PKS genes of *Flavobacterium* sp. JRM (Table 1). Thus, not only the 16S rRNA genes but also the PKS genes are closely related, which is evidence in favor of synonymy of *Flavobacterium* sp. 43-09 and *Flavobacterium* sp. JRM. In addition, among similar sequences, the genes for the synthesis of antibiotic corallopyronin and disorazol (Table 2) were discovered, but the homology with these genes was only 56–57%. Currently, there is no information on the synthesis of secondary metabolites by *Flavobacterium*. In the genome of *Flavobacterium* sp. TAB 87 isolated from Antarctic sea samples, two clusters of the genes of PKS types I and III were found [24]. Thus, the PKS genes are detected in the genomes

of *Flavobacterium*, but BAS synthesized by these PKS are not described; perhaps they are secondary metabolites with new and unique functions.

For the first time in the genomes of bacteria *S. fonticola*, *P. umsongensis*, *R. tilapiae* and *Flavobacterium* sp. isolated from epilithic biofilms of lake Baikal, PKS genes were identified, which are related to the genes of the biosynthesis of antibiotics (difficidine, erythromycin, curacin, mixalamide, corallopyronin, and myxothiazol) and cytostatics (romidepsin, spiruchostatin, and disorazol). Low percentage of homology (50–83%) with known PKS genes indicates the potential ability of investigated strains to produce a number of new, so far undescribed BAS. Thus, the studied Baikal strains could be of practical interest for biotechnology. To confirm our assumptions, it is necessary to isolate individual compounds and determine their structure as well as to conduct studies of their biological activity.

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