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THEORETICAL PAPERS AND REVIEWS

Cyanobacterial Cell Division: Genetics and Comparative Genomics of Cyanobacterial Cell Division

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Abstract—Division of cyanobacteria serves as a model for studying division of plant chloroplasts. Analysis of mutants obtained by methods of "forward" and "reverse" genetics underlies effective strategy for studying genetics of cell division in these photoautotrophic prokaryotes. Comparative genomic analysis indicates that some cyanobacterial genes involved in the control of cell division have homologs among cyanobacteria, green algae, and higher plants, some others, only in bacteria, whereas the remaining genes are specific only for cyanobacteria.

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INTRODUCTION

The majority of bacteria are characterized by symmetrical division. Although outwardly it looks simple, bacterial division is a complicated regulated process, many aspects of which are still poorly understood. Studies of the genetic control of bacterial division began with the identification of *Escherichia coli* conditional lethal temperature-sensitive mutations affecting cell division by screening for mutants that form long filaments without septa [1]. Elongation of the cylindrical part of bacterial cell was continued in the absence of division. Identification of bacterial *fts* and other genes [2–5] promoted deeper insight into the cell division process: how the bacterial cell develops membrane-associated FtsZ ring, the intermediate structure during the formation of septum (partition within the cell); how the cell determines the septum position; what is the mode of coordination between division and chromosomal replication; and how the regulation of proteolysis mediates cell division. Many proteins and specific chromosomal parts are located in specific subcellular regions [3, 5]. Bacteria possess specific elements of the cytoskeleton involved in the cell division, which include the FtsZ protein (bacterial homolog of tubulin) [6, 7], coiled structures of the MreB protein resembling the physiological polymer of eukaryotic actin [8], coiled structures of MinCDE proteins [9], and intracellular profilaments containing the bacterial elongation factor Tu (EF-Tu) [10]. The dividing bacterium utilizes the cytoskeleton structure at the division site for the mechanical construction of the cell. In many species, the key component of this structure is the tubulin-like protein GTPhase FtsZ [11, 12]. The successful realization of this process is dependent on the correct assembly of this protein at the site of subsequent division [13]. After the formation of coiled FtsZ filaments, dozen of other proteins are sequentially supplied to the site of future division for the formation of additional coiled structures [5]. Immunofluorescence microscopy and protein fusion with green fluorescence protein (GFP) were successfully used for the visualization of FtsZ and other cell-division proteins [5, 13]. Most bacterial species are characterized by the fact that the division septum is formed in the middle of the cell. In *Escherichia coli* cells, *minC, minD*, and *minE* are genes that control the choice of this position. In mutants *minC/minD*, the septum formation occurs with equal probabilities at the poles, in the center, and also in positions "1/4" and "3/4" relative to the cell length [14–17]. Processes of the cell cycle, such as DNA replication, segregation of chromosomal copies, and cell division should be strictly coordinated to ensure efficient proliferation. To understand how these processes are controlled in the bacterial cell, it is necessary to identify the complete set of of regulatory genes and to examine their functions.

Cyanobacterial mutants with defective cell division may be helpful in searching for such genes. Cyanobacteria, the ancient relatives of chloroplasts that are similar in structure to Gram-negative bacteria, have photosynthesis of the plant type. Some of them are atmospheric nitrogen-fixing bacteria and are capable of cell differentiation. All methods of molecular genetics can be applied in studies of cyanobacteria [18]. Information about nucleotide sequences of genomes is available for several tens of various strains and species of cyanobacteria (http://www.ncbi.nlm.nih.gov/sutils/grnom table.cgi).

However, the genetic control of cell division in cyanobacteria is studied to a lesser extent than in heterotrophic bacteria. Research in this direction has been activated after the identification of novel cyanobacterial genes *ftn2* and *ftn6* of *Synechococcus* sp. PCC 7942 [19]. Understanding the genetic control of cell division in cyanobacteria may help in studying molecular mechanisms of plant plastid division, evolution of plastids, and evolution of the eukaryotic cell. Knowledge gained on mechanisms and regulation of cell division in cyanobacteria has important ecological and biotechnological aspects in the strategy of using these photoautotrophs [20]. Conventional techniques of comparative genomics and bioinformatics can make a major contribution to solving these problems. The objective of our review is to present the latest results in this field of research.

GENETIC APPROACH TO THE STUDY OF CYANOBACTERIAL CELL DIVISION

Which genes are essential for cell division in cyanobacteria? One of the experimental approaches for resolving this question is "forward" genetics, the goal of which is identifying mutant genes responsible for the phenotype of special interest for researchers. Using methods of "forward" genetics, researchers first have been searching for mutants of interest, and identifying novel genes afterward. This approach can be implemented for identifying genes that encode not only structural, but also regulatory proteins. Another approach involves methods of "reverse" genetics and can be implemented when the gene or the protein encoded by this gene is identified by the results of comparative genomic or proteomic analysis. In this case, scientists attempt to highlight the functional significance of the gene by introducing a mutation into this gene.

Even in the first known cyanobacterial mutants with impaired cell division [21–23], two differnt phenotypes were found [22]: filaments rather than single cells, which form regular septa and apparently have disorders at the completion of formation stages and serpent-like cells that are elongated multinuclear cells with an irregular division. A gene, insertional inactivation of which led to the isolation of a mutant belonging to the first type, was identified in *Synechococcus* sp. PCC 7942 [24]. In this work, random cassette mutagenesis was employed, i.e., a random insertion of a gene cassette, which determines antibiotic resistance, into the bacterial chromosome via homologous recombination with genomic restriction fragments linked to this cassette [25]. Later, transposon mutagenesis was successfully employed in studies of cell division control. Mutants of the second, serpentine type were isolated [19, 26] upon the use of transposon Tn*5*-692 in *Synechococcus* sp. PCC 7942.

Transposon mutagenesis in *Synechococcus* sp. PCC 7942 was first conducted through the transfer of Tn*901* from plasmid into the chromosome [27]. Later, transposon Tn*5* was used in *Anabaena* sp. strain PCC 7120 [28]. Its derivatives, for example, Tn*5*-1058 and others proved to be more effective, because they had (1) a stronger promoter of the operon that determines resistance to antibiotics, (2) elevated frequency of transpositions, and (3) *E. coli* replication origin in the transposon, which promoted the mutant gene identification. With this purpose, the genomic DNA of the mutant was cleaved by restriction enzyme that had no recognition site within the transposon; the obtained DNA fragments were then subjected to conversion into the circular form by self-ligation, and these fragments were used to transform *E. coli* cells [29]. On the obtained plasmid used as the DNA template, the PCR product was isolated with arbitrary primers for the transposon ends; sequence analysis of this product allowed the identification of transposon attachment site in the genome of the given mutant.

Transposon Tn*5*-692 was shown to be 100 times more efficient for cyanobacterium *Synechococcus* sp. PCC 7942 than its precursors [19]. Note that among 3000 colonies with transposon inserted into the genome, 39 colonies with altered morphology were found, namely, "spreading" colonies composed of elongated cells. In classical studies, the genes with mutations causing disturbances in the process of *E. coli* cell division were designated *fts* (filamentous temperature-sensitive mutants) [1, 2], whereas these genes were designated *ftn* (filamentous transposon-derived mutants) in cyanobacteria. Mutants FTN2 and FTN6 of *Synechococcus* sp. PCC 7942 are characterized by extremely elongated cells with random division in different sites. The two novel *ftn* genes were identified in these mutants [19]. Gene *ftn2* encodes the protein, most similar to predicted proteins of other cyanobacteria and plants, but *ftn6* encodes the protein specific only for cyanobacteria [19]. The ortholog *arc6* of *ftn2* in plant *Arabidopsis thaliana* also encodes the chloroplast transit peptide. The involvement of this gene in the control of chloroplast division was later confirmed in [30].

Methods of "reverse" genetics were employed in the study of homologous genes encoding cell-division proteins Ftn2 [19, 31] and Ftn6 [19] in cyanobacteria *Anabaena* sp. PCC 7120 and *Synechocystis* sp. PCC 6803. Mutants showed significant disturbances in cell division. However, unlike mutant FTN2 of *Synechocystis* sp. PCC 7942, the corresponding mutants of *Anabaena* and *Synechocystis* could not be obtained in the homozygote state [19, 31], and their cells contained both mutant and normal gene copies.

For identifying other genes involved in the control of cyanobacterial cell division, cells of *Synechococcus* sp. PCC 7942 were repeatedly mutagenized with transposon Tn*5*-692 [26]. Seven loci have been selected for further work: *ftn2* (Synpcc7942_1943) and *minE* (Synpcc7942_0897), whose role in the control of cell division in cyanobacteria has been established recently [19, 31]; *flm3* (Synpcc7942_2006) and *ftn6*

(Synpcc7942_1707) identified as loci involved in the control of cell division [19, 24]; and three genes, Synpcc7942_0653, Synpcc7942_0644, and Synpcc7942_2059, that have not previously been connected with cyanobacterial cell division [26]. Gene Synpcc7942_0644 encodes the CikA protein, the regulator of circadian clock in cells of *Synechococcus elongatus* PCC 7942 [32]. Gene Synpcc7942_0653 termed *cdv1* [26] encodes peptidyl-prolyl-cis/trans-isomerase, whereas gene Synpcc7942_2059 termed *cdv2* [26] encodes cell-division protein SepF.

The currently known genes responsible for the control of cell division in cyanobacteria are listed in the table.

GENOMIC APPROACH TO THE STUDY OF CYANOBACTERIAL CELL DIVISION

Mutational analysis and comparative genomic analysis allowed an expansion of the range of genes controlling cell division in *Synechococcus* sp. PCC 7942. It was established that cyanobacteria have homologs among genes earlier identified in *E. coli: ftsE, ftsI, ftsK, ftsQ, ftsW, ftsZ, minC, minD*, and *minE* [26, 31, 33]. Genetic studies of *Synechococcus* and *Synechocystis* confirmed that products of other six genes, namely, *ftn2, ftn6, cdv1, cdv2, cdv3*, and *sulA* are involved in the process of cell division [19, 26, 34] (table). The gene encoding the ortholog of protein FtsZ has thus far been cloned and sequenced only from cyanobacterium *Anabaena* PCC 7120 [33,35]. This protein resides in vegetative cells [36], developing the coiled structure [7], and some amount of FtsZ is present in nondividing differentiated cells, which were termed heterocysts. This protein is assumed to execute the cytokinetic function [7]. Gene *ftsZ* has been inactivated in cells of *Synechococcus* sp. PCC 7942 and *Synechocystis* sp. PCC 6803 [37]. The mutation leads to lethality, since only those cells survive that contained both mutant and wild-type allele. An example of considerable success in employing methods of "reverse" genetics to determine gene functions in the control of chloroplast division is the directed mutagenesis in plant homolog of the bacterial protein FtsZ [38]. This protein was shown to possess the chloroplast transit peptide, and subsequent studies revealed that, in contrast to most bacteria encoding the single protein FtsZ, *Arabidopsis* and other plant species contain two different FtsZ proteins located in chloroplasts. It was revealed that both these proteins are located in the chloroplast division region of plants *Arabidopsis*, pea, and tobacco [39].

Methods of comparative genomics allowed the identification of novel genes common for cyanobacteria and plastids that are involved in the control of cell division. The hypothesis claiming that plastids originated from symbiotic cyanobacteria was first advanced in 1905 by the Russian scientist K.S. Mereschkowsky [40]. According to the currently accepted views, plastids originated from a cyanobacterial endosymbiont more than 1.2 billion years ago. In the course of establishing symbiotic relationships, cyanobacteria lost most of their genes, many of which were transferred to the nuclear genome [41]. According to the latest estimates, 16–18% of plant nuclear genes were derived from cyanobacteria [42]. Among them, those genes were detected that control chloroplast division and encode proteins: Arc6, ARTEMIS, and GC1 (also referred to as AtSulA); and ptCpn60α, ptCpn60β [19, 30, 34, 43, 44, 49] (table).

The plant nuclear gene *arc6* is related to the cyanobacterial gene *ftn2* [19, 30], and their orthologs have been detected only in cyanobacteria, eukaryotic algae, and higher plants. Gene *arc6* was identified via cloning from mutant *arc6* [30, 45]. The protein ARC6 is a component of the chloroplast inner membrane and operates as a positive regulator of Z-ring formation [30]. The fused ARC6-GFP protein is located in the coiled structure situated in the plastid center [30]. ARC6 and Ftn2 are proteins with the conservative N-terminal J domain, which may point to their chaperone function. Mutant *arc6* has short filaments of the FtsZ protein within the single large chloroplast. Mutant plants with enhanced synthesis of the ARC6 protein have numerous FtsZ filaments that generate coiled structures around the large chloroplast. The N-end of the ARC6 protein is localized in the chloroplast stroma [30], and its conservative J domain interacts with the CORE domain of the AtFtsZ2-1 protein [46]. In *E. coli* cells, the CORE domain of the FtsZ protein interacts both with FtsA and with ZipA protein involved in the control of FtsZ protein polymerization. Homologs of genes *ftsA* and *zipA* were not detected in genomes of cyanobacteria and higher plants, and, probably, proteins Ftn2/ARC6 may play the same role in stabilization or anchorage of the FtsZ ring in the cytoplasmic membrane as proteins FtsA and ZipA [47].

The ARTEMIS (*Arabidopsis thaliana* envelope membrane integrase) protein was identified via transposon mutagenesis during a search for proteins involved in biogenesis of *Arabidopsis* chloroplasts [43]. Mutant plants were shown to have growth characteristics similar to those for wild-type plants, but ultrastructral analysis revealed elongated, duplicated, and triple nondividing chloroplasts. Meanwhile, when the outer membrane was incapable of terminating the division, thylakoid membranes had the ability to divide in the chloroplast center, between its two halves. The ARTEMIS protein is unique in the molecular structure, combining the C-terminal domain, which resembles the Alb3 and Oxa1 proteins with conservative elements of translocase YidC, and the N-terminal domain, similar to the receptor of protein kinases. Compatative genomic analysis conducted with the use of the YidC/Alb3-like translocase domain sequence, the key sequence in the search for homology, allowed the identification of the homolog protein ARTEMIS in cyanobacterium *Synechocystis* sp. PCC 6803 (gene

Genes involved in the control of cell division in cyanobacteria exemplified by *Synechococcus* sp. PCC 7942

Gene	Protein	Function	Reference	Homolog in the bacterial genome	Homolog in the *Arabidopsis* genome
_2378	FtsZ	GTP-associating cell-division protein; development of the septum-forming ring	[11]	FtsZ	FtsZ1-1 AT5G55280 FtsZ2-1 AT2G36250
_2377	FtsQ	Cell-division protein	[54]	FtsQ	None
_0580 _0482	FtsI	Peptidoglycan glycosyltransferase	[55]	FtsI	"
_0564 _1414	FtsE	Cell-division protein	[56]	FtsE	"
_1104 _0324	FtsW	Cell-division protein	[57]	FtsW	"
_2580 _2468 _2073	dnaK	Heat-shock protein	[58, 59]	dnaK	CPHSC70-1 (chloroplast heat shock protein 70-1 NP_194159.1
_1943	Ftn2	Possibly chaperone	[19, 30]	None	Arc6 AAQ18646/ARC6
_1707	Ftn6	Hypothetical protein	[19]	None	None
_0897	MinE	Specific cell division topology factor	[17, 60]	MinE	AtMinE1 AT1G69390 BAB79236
_0896	MinD	Protein determining the septum formation site	[17, 60]	MinD	MIND AT5G24020
_2001	MinC	Inhibitor of septum formation	[17, 60]	MinC	None
_0653 cdv1	Cdv1	Peptidyl-prolyl-cis/trans-isomerase (rotamase)	[26]	None	CYP38 (Cyclophilin 38); peptidyl-prolyl-cis/trans-isomerase AT3GO1480
_0644	CikA	Sensor histidine kinase, the regulator of circadian clock	[26, 32]	Various histidine kinases (Blast Score is 98-160 bits)	AHK3 NP_564276
_2059 cdv2	sepF	Presumably stimulates Z-ring formation through linking ftsZ protofilaments	[26]	BSU15390 *B. subtilis*	None
_2006 cdv3	Hypothetical protein	Unknown	[24, 26]	None	"
_1617	YidC NP_441564.1	Member of protein family Alb3/Oxa1/YidC	[43]	"	*ARTEMIS* locus of *Arabidopsis* NP_173858, chloroplast envelope membrane integrase
_2477	SulA	Nucleoside-diphosphate epimerase	[34]	SulA	(GC1) (Giant chloroplast1); NP_565505
murC _1741	UDP-N-acetyl-muramate-L-alanine ligase	Cell wall formation; synthesis of peptidoglycan	[61]	*E. coli* ZP_03071496	None
murE _1484	UDP-N-acetyl-muramoyl-alanyl-D-glutamate-2,6-diamino-pymelate ligase	Cell wall formation; synthesis of peptidoglycan	[61]	NP_414627.1	"
murD _1667	UDP-N-acetyl-muramoyl-L-alanyl-D-glutamate synthetase	Biosynthesis of peptidoglycan; cell wall formation	[61]	NP_414630	"
murI _2361	Glutamate-racemase	Conversion of L-glutamate into D-glutamate, a component of peptidoglycan	[61]	NP_418402	"

slr1471). The deletion mutant for gene *slr1471* ensured the formation of tetrameric or hexameric cell clusters, which indicated disturbances in cell division at late stages [43]. Evolutionary and functional relationship of these proteins is confirmed by the data on complementation of mutant *slr1471* with the gene encoding the YidC/Alb3-like domain of the ARTEMIS protein [43].

The gene of giant chloroplast (GIANT CHLOROPLAST 1, GC1, also named AtSulA) was identified on the basis of the similarity of the encoded protein to the assumed cell division inhibitor SulA in *Anabaena* sp. PCC 7120 (*all2390*) and in *Synechocystis* sp. PCC 6803 (*slr1223*) [44, 48]. Gene GC1 is localized at *Arabidopsis* chromosome II and codes for the protein with the N-terminal chloroplast transit peptide that is absent in the cyanobacterial homolog protein. A phylogenetic analysis of homologs of gene GC1 revealed its clear cyanobacterial origin. Analysis of the *Synechocystis* mutant carrying deletion in *slr1223* showed that this gene is vital to the cell [48]; in microscopy studies of heterozygous mutant clones, up to 40% of cells were registered that began to promote cell division, but were incapable of terminating the division. The GC1 protein is associated with the chloroplast inner membrane; its exact function is still unknown.

Chaperonin proteins ptCpn60α and ptCpn60β are required for correct division of chloroplasts in *Arabidopsis thaliana*. These proteins were identified by the method of "forward" genetics in studies of mutants impaired in plastid division [49]. Phylogenetic analysis revealed that both ptCpn60 proteins originated from ancestral cyanobacterial proteins and exhibit resemblance to the GroEL chaperone. The phenotype of filamentous cells in *groEL* mutants of *E. coli* [50], *Caulobacter crescentus* and *Streptococcus* [51, 52] testifies in favor of the assumption that the GroEL chaperone is involved in bacterial cell division. Note that the level of GroEL protein essentially increased in cell division mutants (FTN2 and FTN6) of *Synechococcus* sp. PCC 7942 [53].

Despite the importance of cyanobacteria as model organisms for studying molecular mechanisms of plastid division, there are still few works devoted to the identification of new components of the cell division apparatus [19, 26, 43, 48]. It should be emphasized that using cyanobacteria is a significant advance in this field of researh, because they can be easily cultivated, have a shorter generation time period, and provide an opportunity for obtaining synchronized cultures with the employment of many well-developed genetic tools for the study of cyanobacteria [18].

CONCLUSIONS

Study of the genetic control of cell division in cyanobacteria helps to understand molecular mechanisms of plant plastid division and to examine their evolution. Analysis of cyanobacterial mutants underlies the strategy for studying genetics of cell division. Highly efficient transposon mutagenesis allows the identification of novel genes controlling this process. By comparative genomic analysis, some cyanobacterial genes involved in the control of cell division were shown to be homologous to genes of cyanobacteria, green algae, and higher plants, while some others were encountered only in bacteria, and the remaining genes were specific only for cyanobacteria. Future research will provide answers to many questions. The complex approach combining methods of genetics, genomics, transcriptomics, and proteomics will contribute to better understanding of the genetic control and molecular mechanisms of cell division in cyanobacteria.

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