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REVIEWS

Comparative and Evolutionary Aspects of Cyanobacteria and Plant Plastid Division Study

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Abstract—The review summarizes the current understanding of cyanobacterial cell division mechanisms in comparison with those of eukaryotic plastids. It also sheds light on the present knowledge of the nature of evolutionary transformations of the cyanobacterial cell division apparatus that could have occurred during the establishment of modern plastid division complex. Peculiar properties of cyanobacterial cell division process are discussed as well as the features of primary and secondary plastid replication.

Keywords: cyanobacteria, higher and lower plants, mutants, cell division, chloroplasts

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INTRODUCTION

One of the first experimental works devoted to the physiology of plant plastids was carried out by V.E. Semenenko on chloroplasts of *Selaginella cuspidata* in 1954 [1]. The scientists paid considerable attention to the study of all aspects of plant plastid physiology and development. However, until now the mechanisms of division of these organelles are poorly studied. In the study of the genetic control of the higher plant plastid division cyanobacteria seem to be a convenient choice as a model system.

Cyanobacteria represent a monophyletic group of photoautotrophic bacteria that are of great importance both in nature and in human life [2]. This group of organisms has its own peculiarities of cell division mechanisms. Cyanobacteria are of particular interest because, according to the endosymbiotic theory, all kinds of modern eukaryotic plastids arose from their ancestral progenitor. It is of importance that, the establishment of stable endosymbiotic interactions depends on a developed system of control over processes of endosymbiont cell division and its daughter cell segregation during host cell division [3]. Particularly, the endosymbiotic theory is supported by the facts such as impossibility of de novo plastid biogenesis, presence of autonomous genetic system in plastids, and a similarity between modern plastid division and binary fission of prokaryotic cells.

Some specific features of bacterial cytokinesis are readily traced in the mechanisms of modern plastid division. This confirms the importance and prospects of studying and in-depth consideration of the system of cyanobacterial cytokinesis. Due to the identification and functional analysis of the components of plastid and cyanobacterial cell division, a whole picture of the evolution of plastid division mechanisms at the molecular level is gradually formed [4].

The review outlines the current understanding of the mechanisms of cyanobacterial cell and plastid division in comparative aspect. Moreover, the hypotheses describing putative conversion pathways of the division apparatus of ancestral cyanobacterial endosymbiont into a modern division complex of plastids are discussed.

THE ORIGIN OF PLASTIDS: PRIMARY AND SECONDARY ENDOSYMBIOSES. PLASTID DIFFERENTIATION IN VASCULAR PLANTS

The beginning of plastid evolution, the key organelles of plants, algae, and some other organisms, is traced from the act of endosymbiosis between a heterotrophic eukaryote (host cell) and a photoautotrophic cyanobacterium that occurred about 1 billion years ago [5, 6].

The relatively early event in plastid evolution was a great reduction of the endosymbiont's genome size: plenty of genes were either relocated to the host cell nuclear genome or lost [7]. Gene transfer coupled with the preservation of functions of encoded products would not be possible if a system of transport of the corresponding protein (now translated in the cytosol) across the plastid envelope membranes had not developed [4].

In vascular plants (Tracheophyta), different types of plastids originate during the differentiation of proplastids present in meristematic tissues. Algae and mosses have only one type of plastids, chloroplasts. Thus, a diversity of plastid types within a single organism became apparent only during evolution of vascular plants [8].

Along with Archaeplastida with their primary plastids, direct descendants of endosymbiotic cyanobacteria, some groups of eukaryotes have secondary plastids that arose later due to the secondary endosymbiosis, i.e. engulfing of developed archaeplastid algae (already bearing primary chloroplasts) by eukaryotic cells.

Primary plastids are bound by two membranes; plastids of glaucophytes retain the peptidoglycan layer between these membranes [9]. Two eukaryotic lineages, Chlorarachniophyta and Euglenida, bear secondary chloroplasts arosen in an endosymbiosis with a green alga ("green" secondary chloroplasts). As a result of the secondary symbiosis between the ancestor of Chromalveolata and a red alga, "red" secondary chloroplasts have emerged. The secondary plastid envelope contains 3 or 4 membranes depending on whether or not the cytoplasmic membrane of the endosymbiont-eukaryote was lost [9]. Thus, within a secondary plastid the compartment bounded by the inner membrane pair corresponds to the primary chloroplast. Division of secondary plastids is of special interest; however, the elucidation of its molecular mechanisms was only recently initiated. Since tertiary chloroplasts are extremely rare, almost nothing is known about the mechanisms of their division.

As a result of the second event of primary endosymbiosis yielding plastids, chromatophores of the amoeba *Paulinella chromatophora* (Cercozoa, Rhizaria) have arisen [9] (see below). Due to the relative novelty of this act of endosymbiosis, the study of *P. chromatophora* is undoubtedly important for the development of different aspects of the endosymbiotic theory.

COMPONENTS OF DIVISION COMPLEXES OF CYANOBACTERIA AND HIGHER PLANT CHLOROPLASTS

Like most bacteria, modern plastids divide by binary fission. In the site of division, a constriction appears; its deepening ends by fusion of both envelope membranes. In many prokaryotes and chloroplasts, the fundamental role in this process belongs to the protein FtsZ that forms an FtsZ-ring in the plane of future division. In bacteria, invagination of the cytoplasmic membrane is coupled with the ingrowth of the cell wall into the cell cytoplasm. In higher plant chloroplasts, a coordinated constriction of both envelope membranes occurs in the division plane [10].

However, it is worth mentioning that multiple division is characteristic of plastids in some cases. For cyanobacteria, given a great diversity of their morphology, various cell division patterns distinct from binary fission are also known.

Along with the FtsZ-ring and associated proteins, several additional structures, such as electron-dense plastid-dividing rings (PD-rings) and the dynamin ring, form at the division site of higher plant chloroplasts (and some other plastids) [8].

Since higher plant chloroplasts (like all plastids) are evolutionary successors of the ancestral cyanobacterial endosymbiont, their division complex has still contains certain components of the cyanonacterial cytokinetic system along with the system developed by the host cell.

Extending of the list of division factors of extant cyanobacteria occurs both by the detection and analysis of supposed homologs of known *Escherichia coli* and *Bacillus subtilis* division genes in cyanobacterial genomes and by experimental identification of the new genes in genetic experiments with cyanobacteria. The second way enables identification of division proteins absent in other bacterial groups. It is also important that cyanobacteria have long been the subject of molecular genetic studies, a wide range of methods being now available to identify and study the genetics of these organisms [11].

Division Factors Common for Cyanobacteria and Higher Plant Chloroplasts

This section discusses the division proteins of higher plant chloroplasts, the origin of which goes back to the cyanobacterial endosymbiont.

FtsZ protein. The FtsZ protein is the first identified division factors of eukaryotic plastid division. Encoded in the cell nuclear genome, plant FtsZ is a homolog of bacterial division protein FtsZ [12, 13].

Bacterial FtsZ was initially identified during the analysis of *fts* (filamenting temperature-sensitive) mutants of *E. coli* [14]. All *fts* mutants are characterized by disturbances in cytokinesis expressed in the formation of filaments by mutant cells. Among prokatyotes, FtsZ is present in most bacteria and in some branches of archea [15]. FtsZ is a GTPase with a structural homology to eukaryotic tubulin.

In bacteria, FtsZ molecules polymerize into the ring structure attached to the internal surface of the cytoplasmic membrane [16]. Just this FtsZ-ring marks firstly the site of cell division and is a center for the concentration of other division proteins [17].

The first plant (plastid) *ftsZ* gene was identified in 1995 [12]. It was one of the nuclear *ftsZ* genes of the model higher plant *Arabidopsis thaliana*. Later, it became evident that this protein is present in a number of photosynthetic eukaryotes. The involvement of FtsZ proteins of plants and algae in plastid division is supported by the fact that artificial reduction of this protein level resulted in a sharp decrease in the number of plastids, which became very large [13]. Later, it

was shown that a supramolecular ring structure of FtsZ protein is formed at the plastid division site [18]. The chloroplast FtsZ-ring is located at the stromal side. In most bacteria, including cyanobacteria, there is a single copy of the *ftsZ* gene, whereas in algae and plants there are several *ftsZ* genes. The encoded proteins belong to two families: FtsZ1 and FtsZ2 [13]. FtsZ1 and FtsZ2 in *A. thaliana* demonstrate similar localizations even when the expression level or the assembly pattern of each of them is changed [19]. Both proteins are GTPases and produce heteropolymer filaments in vitro [20]. One of the differences between FtsZ1 and FtsZ2 is that FtsZ2, like most bacterial FtsZs, has a short C-terminal motif (C-terminal core domain), that is not present in FtsZ1. In the *E. coli* cells, this FtsZ domain interacts with FtsA and ZipA proteins controlling FtsZ filament assembly; however, these proteins are absent in cyanobacteria and photosynthetic eukaryotes [8]. It was found that the C-terminal core domain of plant FtsZ2 interacts with ARC6, whereas FtsZ1 interacts with ARC3 protein [21, 22].

Proteins Ftn2 – ARC6, PARC6. The *arc6* mutant of *A. thaliana* was described in the 1990s. In the leaf mesophyll cells of this mutant, only two extremely large chloroplasts are present [23]. A decade later, on the basis of the results of *arc6* mutation mapping, it became clear that the cause of the disturbance in chloroplast division was an impairment of a nuclear gene, which is orthologous to the cyanobacterial gene *ftn2*, essential for the normal cell division progression in cyanobacterial cells [24].

Cyanobacterial *ftn2* mutants demonstrate strong disturbances in cell division. Thus, in the colonies of *Synechococcus* sp. PCC 7942 mutants, there are some cells with the length exceeding that of wild-type cells almost 100-fold [24]. A comparative proteomic analysis of *ftn2* mutant cells enabled identification of more than forty different proteins showing altered expression pattern [25]. This indicates that division damage in these mutants may result in various disturbances of cell physiology. The *ftn2* mutant demonstrates serious changes in the cell ultrastructure [26]. Cyanobacterial Ftn2 is an integral protein of the cell membrane; it is localized in the cell division site and interacts with FtsZ [27]. Similar pattern was observed in higher plant chloroplasts: ARC6 spans the internal membrane in the chloroplast division site, its stromal fragment binds Fts2 via the C-terminal core domain of this protein [21, 28]. The Ftn2 homologs are present only in cyanobacteria and in "green" branch of eukaryotes (Viridiplantae) [24, 28].

Proteins Ftn2 and ARC6 have a N-terminal J-domain extending, in the case of ARC6, into the stroma [24, 28]. For other DnaJ-family proteins, this N-terminal domain is shown to interact with the molecular chaperone HSP70 [29]. However, the interaction between Ftn2 or ARC6 with HSP70 still awaits experimental evidence. DnaJ-domain of cyanobacterial Ftn2 is important for the interaction of this protein with FtsZ in vitro [27].

N-terminal fragment of the plant ARC6 is involved in the recruiting of protein PDV2, specific for higher plants, to the division site. These proteins were shown to interact in the intermembrane space [30]. In *arc6* mutants, short desorganized FtsZ filaments developed. On ARC6 overexpression, FtsZ filaments prove very long; they produce numerous FtsZ-rings. Thus, ARC6 seems to stimulate FtsZ filament assembly and/or be involved in their stabilization [28].

In vascular plant genomes, genes encoding ARC6-like protein of the inner membrane – PARC6 – involved in the chain/cascade of events on late stages of plastid division were found. Being different from ARC6, which binds with FtsZ2 and facilitates FtsZ polymerization, the PARC6 protein interacts with ARC3 and, in contrast, suppresses FtsZ assembly [31].

MinC, MinD, and MinE proteins. Division of chloroplasts and some non-green plastids is usual strictly symmetrical like that of most bacteria. This is ensured by the positioning of the plastid FtsZ-rings on the equator of the organelle.

In bacteria, the Min-system is involved in FtsZ-ring positioning. The MinC protein forms the functional complex with the MinD protein, which inhibits the FtsZ-ring assembly in the area outside the equatorial zone. In the *E. coli* cells, such spatial specificity of MinCD complex depends on the MinE protein, which repels MinCD from the midcell, inducing its oscillation from one cell pole to another. In *B. subtilis*, MinE protein is absent, and MinCD complex does not undergo such oscillations. In this bacterium, the complex is concentrated near the cell poles; the DivIVA protein attaches MinCD to the corresponding membrane regions. Thus, the mechanisms of spatial regulation of FtsZ-ring assembly in Gram-positive and Gram-negative bacteria differ [17].

Cyanobacteria possess all three Min proteins. However, they also have DivIVA-like protein, Cdv3. All four proteins are shown to operate in cell division. Therefore, it is clear that the mechanism of cell division spatial control in cyanobacteria is much more complex than that of *E. coli* and *B. subtilis* [27, 32].

The homologs of bacterial *minD* and *minE* genes were found in the nuclear genome of *A. thaliana* [33, 34]. By means of the reverse genetics methods, *A. thaliana* MinD and MinE proteins were demonstrated to be involved in the determination of the site of plastid FtsZ-ring assembly [33, 34]. Localization of plant proteins MinD and MinE resembles that of MinD in *B. subtilis* cells [35]. Most recently, it was shown that expression of *minD* and *minE* genes is controlled by the cell cycle of the host cell [36].

The MinC protein is not so widespread. It is found only in the moss *Physcomitrella patens* and in some algal lineages [37].

In *A. thaliana,*ARC3 and MCD1 proteins of eukaryotic origin participate in the control of plastid FtsZ-ring localization along with MinD and MinE.

ARC3 protein. ARC3 protein was found only in the members of "green" branch of Archaeplastida. In *A. thaliana*, it is localized in the chlroplast stroma; its protein chain consists of an FtsZ-like domain fragment and MORN (membrane occupation and recognition nexus) motif [38]. ARC3 overexpression arrests chloroplast division owing to inhibition of FtsZ assembly. This ARC3 feature resembles that of MinC [22]. ARC3 is shown to interact with FtsZ1, MinD, MinE, and PARC6; it is localized at the chloroplast division site and on its poles [22, 31, 38]. The *arc3* mutant contains one large chloroplast; in its stroma, several FtsZ-rings are present (like in the *minD* mutant of *A. thaliana* and bacterial *minC*- and *minD* mutants). Apparently, ARC3 took over the role of this protein during the evolution of modern plants (lacking MinC protein) [22].

Other genes and proteins. In addition to the aforementioned genes, inactivation of some other genes of cyanobacterial origin results in disturbances of chloroplast division. Among these are the following genes: *GC1* (also named as *AtSulA*), *CRL*, *CPN60*, *ARTEMIS*, *YlmG*, and *mur*. So far it is unknown whether these gene products participate in plastid division directly or indirectly.

***GC1* and *SulA* genes.** The *GC1* gene was identified on the basis of the similarity of the encoded protein to cyanobacterial SulA protein [39, 40]. In *E. coli*, SulA inhibits FtsZ-ring assembly in the event of SOS-response, thus preventing cell division [17]. Up to 40% of incompletely divided cells are observed accumulated in the colonies of heterozygous *sulA* mutants of *Synechocystis* sp. PCC 6803 [40]. Plant mesophyll cells with artificially decreased GC1 level have a single or two "giant" chloroplasts [39]. The GC1 protein is attached to the inner chloroplast membrane; its function is not determined precicely yet. The secondary structure of this protein shows a high similarity (80–90%) to epimerases; its substrates are activated monosaccharides [39]. However, so far there is no information confirming that GC1 has epimerase activity. Only additional experiments will enable to elucidate a role of SulA/GC1 in the cyanobacterial/plastid division process. Note that an increasing number of the new experimental data suggest that enzymes may acquire a new function during evolution, which allows them to participate in the formation of the bacterial cell cytoskeleton and division [41].

***CRL* gene.** In the *crl* mutant, severe defects associated with the inhibition of chloroplast division were observed in mesophyll cells, and these defects were found to be coupled with disturbances of cell division and differentiation. CRL protein is localized in the plastid envelope and could participate in the signal transduction associated with plant development [42]. Functions of cyanobacterial CRL counterpart have not been analyzed thus far.

***CPN6* genes.** Proteins-chaperonins ptCpn60α and ptCpn60β are essential for normal division of *A. thaliana* chloroplasts [43]. The phylogenetic analysis showed that both these proteins are closely related to the cyanobacterial chaperone GroEL. The involvement of GroEL in the bacterial cell division is confirmed by the formation of filamentous phenotype in strains bearing mutations in the corresponding locus [44]. Noteworthy, GroEL level is substantially elevated in *ftn2* and *ftn6* mutants of *Synechococcus* sp. PCC 7942 [25].

***ARTEMIS* gene.** In the cells of *Arabidopsis artemis* mutant, elongated non-dividing chloroplasts with two or three lobes are present [45]. ARTEMIS protein is an integral protein of the inner chloroplast envelope membrane. It has unique molecular structure, combining a C-terminal domain similar to Alb3 and Oxa1 proteins comprising conserved elements of YidC translocase and an N-terminal domain similar to receptor protein kinases. A comparative genomic analysis by means of homology search for YidC/Alb3-like translocase domain enabled the identification of the homologous protein in the cyanobacterium *Synechocystis* sp. PCC 6803 (*slr1471* gene). The deletion mutation in *slr1471* gene results in the formation of tetrameric or hexameric cell clusters, which is indicative of disturbances in the progression of the late stages of cell division [45]. Evolutionary and functional similarity of cyanobacterial and plant proteins is confirmed by the complementation of cyanobacterial *slr1471* mutation by the gene encoding YidC/Alb3-like domain of the ARTEMIS protein [45].

***YlmG* gene.** The YlmG protein may also be related to cyanobacterial and chloroplast division. In Gram-positive bacteria, the *ylmG* gene is positioned in the cluster of cell division genes following the *ftsZ* gene. Overexpression or deletion of *ylmG* gene in *Synechococcus* disturbs both cell division and nucleoid structure. Overexpression of AtYlmG in *A. thaliana* results in the formation of the irregular network of chloroplast nucleoids along with disturbances in chloroplast division, whereas reduced expression of this gene is coupled with nucleoids clustering in several sites but does not affect chloroplast division [46].

***Mur* genes.** Since peptidoglycan layer is absent from the chloroplast envelope of higher plants, it is tempting to assume that genes involved in its synthesis in the cyanobacterial endosymbiont should be absent in plant genomes. However, the analysis of the genome of the moss *P. patens* revealed the presence of nine homologs of bacterial genes involved in the synthesis of the periplasmic peptidoglycan-containing cell wall. Inactivation of some of them (*PpPbp, PpMurE, PpMurA*, and *PpMraY*) results in defects of chloroplast morphology and variation of their number [47]. Earlier, it has been shown that penicillin suppresses chloroplast division in this moss, whereas the antibiotic does not affect higher plant chloroplasts

[48]. In the *A. thaliana* genome, five homologs of *mur* genes were found [47]. However, they are apparently not related to chloroplast division [49].

Thus, a number of components inherited from the ancestral cyanobacterial endosymbiont are involved in the process of modern chloroplast division. Many of them perform functions similar to that of homologous elements of the cytokinesis system of extant cyanobacteria.

Division Complex of Higher Plant Chloroplasts: Components of Eukaryotic Origin

Among known structural components of eukaryoric origin involved in the higher plant chloroplasts division, there are the outer PD-ring (glucan filaments + PDR1 protein) and DRP5B, PDV1/2, ARC3, and MCD1 proteins. The inner PD-ring also belongs to these components because such a structure is absent in cyanobacteria.

The emergence of genes-paralogs has played an important role in the formation of the modern plastid division apparatus. One group of such genes comprises paralogous FtsZ proteins. One of these paralogs (FtsZ1 – arisen from the ancestor of the "green" branch paralogs) is supposed to have lost its C-terminal core domain during evolution, and that is probably why their functional divergence has occurred. The phylogenetic analysis shows that similar events have also occurred during the "red" branch (Rhodophyta) evolution and secondary "red" chloroplasts development [13, 50]. PARC6 and PDV1 proteins are paralogs of ARC6 and PDV2 proteins, respectively. The duplication of corresponding genes is believed to have taken place in the ancestor of vascular plants (Tracheophyta).

PD-rings. Participation of plastid-dividing rings is typical of the division of different plastids, including higher plant chloroplasts. PD-rings are readily identified, and, as a rule, there are two of these present. The outer plastid-dividing ring consists of filaments 5–7 nm in diameter and is positioned on the cytosolic side of the chloroplast, encircling the division site. The inner plastid-dividing ring has the form of circular belt with a width of 5 nm; it is secured to the inner envelope membrane from the stromal side [8, 51, 52]. In the unicellular alga *Cyanidioschyzon merolae*, the third (middle) PD-ring is present in the intermembrane space of the chloroplast envelope [8].

By proteomic analysis, it was shown that the outer PD-ring is a bundle of polyglucan filaments associated with glycosyl transferase PDR1 [53]. PDR1 is assumed to participate directly in the synthesis of polyglucan filaments of the outer PD-ring. The inner and middle PD-rings composition so far remains unknown [8].

DRP5B protein. Identification of dynamin-like DRP5B protein was facilitated by the studying of its homolog in the red alga *C. merolae* and the analysis of *A. thaliana* mutation in this gene (*arc5* mutant) [54, 55]. *DRP5B* is the first identified genes of eukaryotic origin that are thought to be involved in plastid division.

Molecules of the dynamin family members, all of which are GTPases, are capable of forming spiral structures on the surface of artificial membranes, and these can elongate the membranes into tubes of varying size [56]. In the cell, dynamin assembles into the ring (or into the spiral structure) in the regions limiting clathrin-coated invaginations of the plasma membrane, and this results in the pinching off of vesicles [56]. The members of dynamin family exist only in eukaryotes; however, their distant relatives were found in bacteria as well [57], i.e., it is possible that the common ancestor of dynamins has a bacterial origin.

DRP5B is recruited to the cytosolic side of the chloroplast division complex before its constriction onset [54, 55]. In *A. thaliana*, PDV1 and PDV2 proteins are involved in the DRP5B recruitment [58].

Recently, the plastid division protein DRP5B has also been shown to be involved in peroxisome division [59]. Interestingly, the proteins that are the most closely related to DRP5B are involved in cytokinesis in *A. thaliana* and *Dictyostelium discoideum* [8].

***PVD* genes.** The genes-paralogs, *PVD1* and *PVD2*, were identified in the analysis of mutants with the phenotype resembling that of *A. thaliana arc5* mutant [58]. PDV1 and PDV2 are integral proteins of the outer chloroplast envelope membrane localized at the division site.

PVD2 is present exclusively in higher plants (Embryophyta), whereas its paralog (PVD1) is found in vascular plants (Tracheophyta) only. Both proteins expose their N-terminal regions forming coiled-coil motifs to the cytosol [58]. In the intermembrane space, C-terminal domain of PDV2 interacts with ARC6 protein. It is also shown that, in the absence of PARC6, the PDV1 localization is impaired [31]. It is not yet known whether PDV1 and PARC6 could interact directly with each other.

In the double *pdv1 pdv2* mutants, improper DRP5B localization at the chloroplast division site is observed, whereas inactivation of each of these genes does not disturb the DRP5B localization. Therefore, functions of PDV1 and PDV2 proteins may be suggested to overlap [58]. Thus, PDV proteins participate in the coordination between functioning of stromal and cytosolic components of the division apparatus.

Other proteins. CLMP1, AtCDT1, DDB1, MCD1, and MSL also belong to the group of proteins of eukaryotic origin that are involved in higher plant chloroplast division.

CLMP1 protein. In *Arabidopsis clmp1* mutant, plastid division is arrested at the late stages, so that daughter plastids remain connected by a narrow bridge, PD, FtsZ, and dynamin rings being attached to this bridge. Functional CLMP1 protein is necessary

for the completion of separation of daughter chloroplasts [60].

AtCDT1 proteins. A feature specific to AtCDT1a protein is its localization both in plastids, where it interacts with ARC6 protein, and in the cell nucleus, where it, along with AtCDT1b, participates in nuclear DNA replication. The functional significance of interaction between proteins AtCDT1a and ARC6 is so far unknown. However, by means of RNA interference, a decrease in the amount of AtCDT1 and a simultaneous increase in the nuclear DNA content were found to result in the suppression of plastid division. On the basis of this data, these proteins are assumed to be involved in the coordination of plastid division with the cell cycle progression [61].

DDB1 protein. The role of one of the factors connected to the plastid division in tomato was attributed to the DDB1 protein [62]. However, in the case of *Arabidopsis* seedlings having a mutated version of its homolog, no disturbances in plastid division were reported [63]. The *DDB1* homologs are found in many organisms. Protein complexes containing DDB1 are involved in DNA reparation, ubiquitin-mediated proteolysis, and transcription inhibition.

MCD1 protein. In the chloroplasts of *mcd1* mutant, several constrictions are initiated on a single organelle, which is accounted for by the disturbances in the division spatial regulation system [35]. MCD1 protein is found only in higher plants. It is an integral protein of the inner chloroplast envelope membrane, and is positioned therein in such a way that its coiled-coil motif is located on the stromal side. C-terminal fragment of MCD1 protein has been shown to directly interact with MinD protein, this interaction being required for normal localization of MCD1 [35]. Apparently, MCD1 is one of the components of the chloroplast division site positioning system.

MSL proteins. ***A. thaliana*** MSL2 and MSL3 proteins are localized at the periphery of chloroplast stroma. Double *msl2 msl3* mutants have large spherical chloroplasts, and this must be indicative of an elevated osmotic pressure inside the chloroplasts. MSL2 and MSL3 proteins might control ion exit from plastids in response to an envelope membrane tension increase, which occurs due to forces causing constriction deepening [64]. Thus, these proteins evidently participate in the regulation of plastid size and shape [64]. Recently, it has been also shown that MSL2 and MSL3 proteins are involved in the positioning of the *A. thaliana* chloroplast division machinery [65].

Proteins Involved in Cyanobacterial Cell Division That Have No Homologs in Higher Plants

Modern plastids are semi-autonomous organelles. During their evolution, a requirement in some genes of the cyanobacterial endosymbiont, division genes in particular, had disappeared, and they were permanently lost. The genes connected to cyanobacterial cell division but absent in higher plants are described below.

In the genomes of plastid-bearing eukaryotes, no homologs of the following cyanobacterial cell division genes *ftn6, cdv1*, and *cikA* were found: [32]. The *cdv1* gene encodes a peptidyl-prolyl cis/trans isomerase. The *cikA* gene encodes the circadian rhythms regulator in the *Synechococcus* sp. PCC 7942 cells [66]. Apparently, these genes were lost shortly after the act of endosymbiosis. However, although genes *sepF, ftsI*, and *ftsW* were not detected in higher plant genomes, their homologs are found in the plastid genomes of some algal species. Thus, genes *ftsW* and *sepF* are found in the genome of the glaucophyte *Cyanophora paradoxa*. Plastid genomes of *Nephroselmis olivacea, Mesostigma viride*, and *Chlorokybus atmophyticus* bear genes encoding FtsI and FtsW proteins [37].

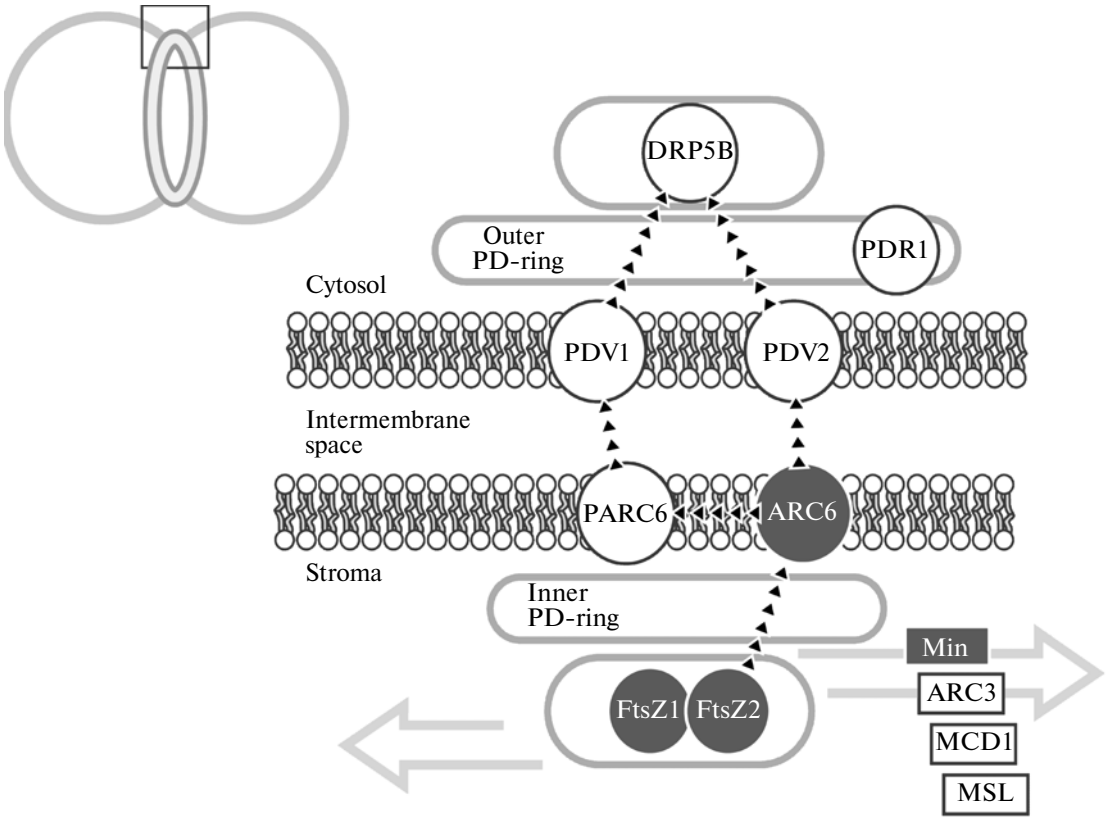
Ftn6 **protein.** The cells of *Synechococcus* sp. PCC 7942 *ftn6* mutant are more than 20-fold longer than those of wild-type strain [24]. The primary structure of Ftn6 makes possible to predict its soluble nature only [32]. The results obtained in vivo are insufficient to predict Ftn6 protein functions; however, in vitro experiments indicated a possibility of its physical interactions with Ftn2 and FtsZ proteins [67]. The *Synechococcus* sp. PCC 7942 *ftn6* mutant cannot form defined rings in spite of the presence of the normal FtsZ content [32]. The proteomic analysis of this mutant revealed several dozens of proteins with altered levels, and this may indicate a pleiotropic character of this mutation and its importance for the cell [25]. The cell ultrastructure of the *ftn6* mutant also demonstrates multiple changes [26].

FtsW and FtsI proteins. The bacterial cell division protein FtsW has 10 transmembrane domains and a long periplasmic loop; both its termini are exposed into the cell cytoplasm. In *E. coli*, FtsW is positioned at the division site and its C-terminus was shown to interact with FtsZ protein. The FtsW protein also interacts with FtsI protein and is required for its correct localization [17, 68]. In bacteria, FtsW protein may coordinate the process of FtsZ-ring formation in the cytoplasm and the synthesis of periplasmic peptidoglycan, an ingrowing cell wall material. The FtsI protein, also named PBP2 (penicillin-binding protein 3), is a transpeptidase which is necessary for the cross-linking of newly formed bacterial cell wall components at the division site [17, 69].

DIVISION COMPLEX ASSEMBLY AND CONSTRICTION: DIVISOME IN ACTION

Assembly of Cyto- and Plastokinesis Complexes

According to the proposed model of the cyanobacterial cytokinesis system [67], the Ftn2 protein is a central player in the attachment of Z-ring to the cytoplasmic membrane and in recruiting other cell division factors to the preformed ring. The involvement of



Scheme of higher plant chloroplast division complex.

Lines of arrowheads designate the sequence (before division act) of recruiting corresponding components. Proteins of bacterial origin are darkened.

Ftn2 in the attachment of FtsZ to the cytoplasmic membrane indicates its homology to the FtsA protein of *E. coli*, which is absent in cyanobacteria and some other groups of prokaryotes. The exceptional importance of Ftn2 in the formation of the division complex architecture is accounted for by its in vitro interaction with division proteins FtsI, FtsQ, Cdv3, SepF, Ftn6, and YlmD, along with FtsZ [67]. In cyanobacteria, FtsZ, Ftn2, Ftn6, and SepF proteins are localized at the division site; Ftn2, Ftn6, and SepF participate in the regulation of FtsZ polymerization. The localization of FtsQ, FtsW, and FtsI proteins in cyanobacterial cells has not been determined experimentally yet; however, it is already clear that these proteins are indispensable for the process [67].

The formation of division complex in the chloroplast occurs in several stages in the following sequence: FtsZ-ring, inner PD-ring, outer PD-ring, and DRP5B-ring [70]. Morphology and the pattern of assembly, constriction, and disassembly of PD-rings are the most thoroughly studied in the red alga *C. merolae* [71] and the model plant *A. thaliana* [10]. It is worth mentioning that the stromal complex affects the assembly of the cytosolic components; in particular, the topological information is transferred from it to the cytosolic complex assembly systems (figure).

Constriction of the Division Site

The identity of factors directly involved in mechanical constriction/retraction of the plastid (bacterial) envelope so far remains the subject of debate. Self-assembling rings of the bacterial FtsZ proteins generate constrictions on the liposome surface [72]. Spiral dynamin structures pull liposomes into membrane tubes [56]. Apparently, only FtsZ and DRP5B contribute to the generation of force required for division.

Like cyanobacteria, plastids contain their own genomes. The mechanisms of plastid DNA replication and segregation and their connection to the plastokinesis process are currently unclear in many respects.

In bacteria, the corresponding processes were studied only in *E. coli* and *B. subtilis*. Since the cells of most bacteria have only a single chromosome, nucleoid replication and segregation are strictly coordinated with the launching of cell division [17]. This mechanism, described in *E. coli*, is called the "nucleoid occlusion." This barrier system inhibits the Z-ring assembly in the cell zones where nucleoids are currently present. As a result, the FtsZ-ring can only form in the midcell, after nucleoid segregation [17].

Cyanobacteria and plastids have several genome equivalents [73]. In cyanobacteria, nucleoids are seg-

regated only at the stage of cytokinesis (immediately before the separation of daughter cells); therefore, daughter cells usually happen to get different number of chromosomes [74]. The plastid division site was shown to be occupied by nucleoids at the onset of division [8].

DIVISION OF OTHER TYPES OF PLASTIDS

More about Primary Plastids

Non-photosynthetic plastids of higher plants. While studying the mechanism of plastid division in vascular plants, one pays much attention to the biogenesis of chloroplasts, whereas the molecular mechanisms of division of other plastids are left poorly covered [8]. This is due to the smaller size of non-green plastids and their poorly understood morphology compared to chloroplasts. For example, numerous tubular bridges (stromules) interconnecting some plastids [75] make the studying of division much more difficult even at the level of electron-microscopic determination of particular organelle boundaries.

For non-photosynthetic plastids of vascular plants, the plastokinesis apparatus is assumed to resemble that of chloroplast division machinery. FtsZ, ARC6, and PVD proteins are localized at the division site in non-green plastids as well. Inner and outer PD-rings were also detected in the region of the division site. However, one should not rule out that other forms of plastid division that do not involve the division complex described might exist [76, 77].

Plastids of Archaeplastida that do not belong to higher plants: cyanelles of glaucophytes. Glaucophytes represent the group of organisms that got separated from the "red-green" branch of archaeplastids relatively early [9]. Therefore, they are of remarkable interest. Chloroplasts of glaucophytes, also named cyanelles, have a peptidoglycan layer in the intermembrane space, and this distinguishes them from plastids of other eukaryotes. This layer is the direct descendant of the cell wall of the cyanobacterial endosymbiont. In plastids of "red-green" branch, outer and inner membranes synchronously move to the cell center during division, maintaining a small space between them over the entire area.

In contrast, during division of glaucophyte chloroplasts, constriction of the inner membrane coupled with the ingrowth of the peptidoglycan layer precedes the invagination of the outer membrane, resembling the pattern of cyanobacterial cell division [78, 79]. The FtsZ-ring forming on the stromal side of the division site is known to be involved in the *C. paradoxa* chloroplast division [79]. The *FtsW* and *SepF* genes were detected in the chloroplast genome of this alga, whereas its nuclear genome encodes MinD and MinE proteins [37]. Furthermore, a structure resembling the inner PD-ring was observed by electron-microscopic analysis of *C. paradoxa* chloroplasts, whereas outer PD-ring was not detected [78, 79]. Plastid division genes of eukaryotic origin, such as *Drp5B*, were not identified among currently available sequences of *C. paradoxa* nuclear genome. Thus, other factors apparently function in the glaucophyte chloroplast division. Substantial help in this matter should be provided by sequencing of *C. paradoxa* nuclear genome and further study of the structure and growth mechanisms of bacterial cell wall (cyanobacterial in particular).

Chromatophores of *P. chromatophora*. The close amoeba *Paulinella chromatophora* is evidently the product of the second (of two currently known) event of primary endosymbiosis. Its cells possess two large elongated chromatophores with a peptidoglycan layer within their envelope [80]. A number of cyanobacterial division genes were identified in the chromatophore genome of *P. chromatophora*, e.g. *ftsZ, ftn2, minC, minD, minE, cdv1*, and *cdv2* genes. Surprisingly, the homolog of the cyanobacterial *sulA* gene is absent in the chromatophore genome [80]. Intriguingly, the *ftn2* gene proved severely altered [80]. Its N-terminus being severely truncated, the Ftn2 of *P. chromatophora* has lost its DnaJ domain, which may have caused a characteristic morphology of chromatophores: they are approximately 20-fold longer than the cells of related cyanobacteria [80]. It is worth mentioning that truncation of *Nostoc* sp. PCC 7120 *ftn2* gene from both ends results in the formation of substantially elongated vegetative cells [24]. Publishing of the complete nucleotide sequence of the *P. chromatophora* nuclear genome is likely to significantly increase our knowledge about the formation of the division apparatus of chloroplasts and other obligate endosymbionts.

Secondary Plastids

The relatively small number of works is devoted to secondary plastid division, but already on this basis, in principle, it is possible to trace the evolution of the structure and functioning of the secondary chloroplast division apparatus.

Electron-microscopic observations of "red" chloroplasts of stramenopiles surrounded by four membranes showed that in the zone of their division in the space between the pairs of membranes there is an electron-dense ring; its localization corresponds to that of the outer PD-ring of primary chloroplasts [81]. In the diatom *Thalassiosira pseudonana*, the DRP5B protein is localized at the chloroplast division site [8]. The *ftsZ* gene is found in the nucleomorph (the remnant of endosymbiont nucleus) genome of cryptophytes [82]. Nuclear genomes of Stramenopiles and Haptophyta have the *ftsZ* gene as well as *MinC, MinD, MinE*, and *Drp5B* genes [37]. Thus, during division of secondary "red" chloroplasts, the components of the division apparatus of primary chloroplasts are still involved in transformations undergone by the inner pair of envelope membranes.

The division mechanism of the secondary chloroplast compartment produced by the outer membrane pair is unknown. At the division site, there were observed no visible structures resembling PD-rings or just attached to these membranes. The division of the outer membrane pair is assumed to occur in a different way compared to that of the inner compartment corresponding to the primary chloroplast and surrounded by the inner membrane pair. In many stramenopiles, the outer compartment divides in the same plane as the inner one, but the constriction of the outer membrane pair does not immediately follows the retraction of the inner compartment.

In *Apicomplexa* (e.g., *Plasmodium*), there are secondary "red" plastids (called apicoplasts) surrounded by four membranes. They have lost a capability to photosynthesize, and their division occurs by successive constriction and subsequent fusion of all four envelope membranes. In the genomes of *Apicomplexa*, none homologs of currently known plastid division genes were found. In *Toxoplasma gondii*, a dynamin-like TgDRPA protein is localized at the division site of apicoplast on its cytosolic surface [83]. This protein is widespread in *Apicomplexa*; however, it is not a descendant of DRP5B protein, although both belong to the dynamin family [83]. Thus, biogenesis mechanisms of apicoplexan's plastids differ from those operating in photosynthetic eukaryotes.

CONCLUSIONS

During development of autotrophic eukaryotes, the prokaryotic endosymbiont experienced a number of structural and functional changes, its division machinery in particular. The comparison between extant cyanobacteria and plastids allows us to reconstruct the sequence of these evolutionary changes. However, the mechanisms of cell division in cyanobacteria and chloroplasts are currently investigated insufficiently. To deepen our understanding of the genetic control of these processes, the studying of new cyto-and plastokinesis mutants and detailed genetic and biochemical assays are required.

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