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REVIEW

Evolution of the chloroplast division machinery

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Abstract **Chloroplasts are photosynthetic organelles derived from endosymbiotic cyanobacteria during evolution. Dramatic changes occurred during the process of the formation and evolution of chloroplasts, including the large-scale gene transfer from chloroplast to nucleus. However, there are still many essential characters remaining. For the chloroplast division machinery, FtsZ proteins, Ftn2, SulA and part of the division site positioning system— MinD and MinE are still conserved. New or at least partially new proteins, such as FtsZ family proteins FtsZ1 and ARC3, ARC6H, ARC5, PDV1, PDV2 and MCD1, were introduced for the division of chloroplasts during evolution. Some bacterial cell division proteins, such as FtsA, MreB, Ftn6, FtsW and FtsI, probably lost their function or were gradually lost. Thus, the chloroplast division machinery is a dynamically evolving structure with both conservation and innovation.**

Keywords chloroplast division, evolution, cyanobacteria

Introduction

Chloroplasts are specialized organelles that carry out photosynthesis and many other important processes such as fatty acid and amino acid biosynthesis in plant cells. Many of the biological pathways in chloroplasts are similar to those in cyanobacteria. Chloroplasts have a small circular genome of about 60–200 genes without associated histones (Gray, 1999; Howe et al., 2003; Raven and Allen, 2003). They have their own protein-synthesizing machinery, which more closely resembles that of prokaryotes than that found in the cytoplasm of eukaryotes (Harris et al., 1994). Molecular phylogenetic studies of the genomic sequences of chloroplasts in many plants and several species of cyanobacteria strongly support the idea that chloroplasts are derived from cyanobacteria (Chu et al., 2004). After the *Arabidopsis* and many other plants' genomes were sequenced, it was revealed that most of the cyanobacterial genes were transferred into the nuclear genome in the past, and that most of them have acquired sequences encoding chloroplast transit peptides (Raven and Allen, 2003; Vesteg et al., 2009; Xiong et al., 2009). Many of the functional proteins of chloroplasts were also found to be homologous to cyanobacterial proteins (Douglas, 1998; McFadden, 1999; Raven and Allen, 2003; Vesteg et al., 2009). Thus, it is now widely accepted that chloroplasts originated from cyanobacteria through endosymbiosis.

Higher plants have many chloroplasts per cell in green tissue. For example, the mature mesophyll cells of wild-type *Arabidopsis thaliana* contain about 80–110 chloroplasts per cell (Marrison et al., 1999). New chloroplasts are generated by binary division of existing chloroplasts (Leech et al. 1981). Chloroplasts divide during cell division and expansion (Possingh, 1969; Saurer and Possingham, 1970; Ellis and Leech, 1985). Dumbbell-shaped chloroplasts, which represent the division phase, can frequently be found in young leaf tissue. Chloroplast division has physiological importance for plant cells. Suppression of chloroplast division results in fewer and larger chloroplasts per cell (Osteryoung et al., 1998; Pyke, 1999). A chloroplast division mutant was reported to have a defect in gravitropism (Yamamoto et al., 2002). Smaller and more numerous chloroplasts per cell provide an advantage compared to larger and fewer chloroplasts: smaller chloroplasts have more total surface area and may exchange materials with other parts of the cell more efficiently. They can also migrate faster in response to changes in light intensity and direction (Jeong et al., 2002).

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Multiple chloroplasts in one cell seem also very important in the history of chloroplast genome evolution: cells with multiple chloroplasts can withstand the breaking of some chloroplasts, leading to the gene transfer from the chloroplast genome to the nuclear genome (Timmis et al., 2004; Cullis et al., 2009). This transfer is important for the establishment of the modern chloroplast and nuclear genomes (Martin, 2003).

Early studies of chloroplast division were limited to observation by either light or electron microscopy. More details of chloroplast division were obtained following improvement of electron microscopy techniques (Leech et al., 1981; Oross and Possingham, 1989; Robertson et al., 1996). Observation of proplastids, which are the progenitor plastid type, reveals a central constriction that has been interpreted to represent the division phase of proplastids. Similar to proplastid division, chloroplast division includes elongation of the chloroplasts to form a peanut shape, constriction of the division furrow, further narrowing of the division furrow to a thin isthmus that joins the two daughter chloroplasts, and finally pinching off of the narrow isthmus. The envelope membranes of daughter chloroplasts are then resealed (Leech et al., 1981; Oross and Possingham, 1989).

Electron-dense deposits are observed at the division site of plastids (Kuroiwa et al., 1998; Kuroiwa et al., 2008). They form ring-like structures on the stromal face of the inner plastid membrane and the cytosolic surface of the outer plastid membrane. They were named the inner plastid-dividing (PD) ring and outer PD ring. A ring-like structure called the middle PD ring is also found between the two envelope membranes of the plastid in some red algae, but not in higher plants (Kuroiwa et al., 1998). The inner PD ring forms first and is belt-like, while the outer PD ring is rope-like and narrower than the inner ring. In the process of the constriction of plastid division furrow, the width and thickness of the outer PD ring increase linearly. The width of the inner PD ring remains the same throughout the plastid division. It has been suggested that the inner PD ring decomposes during constriction, and the outer PD ring wraps around the chloroplast with a constant number of molecules during the constriction (Miyagishima et al., 2001).

To document the division and development of chloroplasts, Leech's group isolated 11 chloroplast division mutants in *Arabidopsis*, and named them *arc*, for accumulation and replication of chloroplasts (Pyke and Leech, 1994; Marrison et al., 1999). In each of the mutants, the mutation is recessive and represent single nuclear locus. Among these mutants, *arc1* and *arc7* have smaller and more numerous chloroplasts while the other nine mutants show larger and fewer chloroplasts. *arc6* shows the most severe phenotype, with only 1–2 chloroplasts per cell (Robertson et al., 1995). *arc5* has about 10 large chloroplasts per cell, which are frequently dumbbell-shaped (Robertson et al., 1996; Gao et al., 2003). *arc3* and *arc11* have about 20 chloroplasts of various sizes per cell (Marrison et al., 1999). Double mutants were made to elucidate the role of some *arc* genes in chloroplast development and division. Based on the phenotypes of single and double mutants, several hypotheses were developed (Marrison et al., 1999). It was suggested that *ARC6* controlled the initiation of both proplastid and chloroplast division; *ARC3* had an important role in the initiation of chloroplast division and controlled the rate of chloroplast expansion; *ARC11* might function just before the initiation of chloroplast division or earlier than the chloroplast expansion phase, and controlled the central positioning of the final division plane; *ARC5* worked in the final stage of chloroplast division and facilitated the separation of the two daughter chloroplasts; *ARC1* was in a different pathway and downregulated proplastid division. However, later cloning of several chloroplast division genes and their further characterization indicated that most of the hypotheses above were inaccurate (Itoh et al., 2001; Gao et al., 2003; Vitha et al., 2003; Fujiwara et al., 2004; Shimada et al., 2004; Maple et al., 2007; Glynn et al., 2008).

With the rapid developments in molecular biology and genomics, many bacterial cell division genes were cloned and the functions of their gene products have been extensively studied (Bramhill, 1997; Rothfield et al., 1999; Errington et al., 2003; Adams and Errington, 2009). Some of the chloroplast division genes have also been cloned recently (Osteryoung and Pyke, 1998; Strepp et al., 1998; Colletti et al., 2000; Itoh et al., 2001; Gao et al., 2003; Vitha et al., 2003; Fujiwara et al., 2004; Maple et al., 2004; Raynaud et al., 2004; Shimada et al., 2004; Miyagishima et al., 2006; Glynn et al., 2009; Nakanishi et al., 2009; Zhang et al., 2009). The results indicated that the chloroplast division machinery has inherited some of the important features of the cyanobacterial cell division machinery and it also has acquired some eukaryotic features from the host cell (Osteryoung and Nunnari, 2003). This review illustrates the conservation and innovation of the chloroplast division machinery during evolution by comparing some of the key components of the division machineries between bacteria and chloroplasts.

Conservation between bacterial cell division proteins and chloroplast division proteins

Since chloroplasts are derived from endosymbiotic cyanobacteria and many chloroplast-targeted proteins also originated from cyanobacteria, it is likely that most of the components of the chloroplast division machinery are derived from the cell division machinery of cyanobacteria (Osteryoung, 2000). Indeed, a search for homologs of bacterial cell division genes in the sequenced *Arabidopsis* genome led to the discovery of several chloroplast division genes: the *FtsZ* gene family, *MinD*, *MinE*, *ARC6* and *SulA* (Osteryoung and Vierling, 1995; Osteryoung et al., 1998; Colletti et al., 2000; Stokes et al., 2000; Itoh et al., 2001; Vitha et al., 2003; Maple et al., 2004; Raynaud et al., 2004).

FtsZ

FtsZ is a GTPase that was first found in *Escherichia coli* and is conserved in almost all bacteria and archaea (Bramhill, 1997; Rothfield et al., 1999). FtsZ is related to tubulin, and is suggested to be the ancestor of tubulin (de Boer et al., 1992a; RayChaudhuri and Park, 1992; Lowe and Amos, 1998; Adams and Errington, 2009). The structures of FtsZ (Erickson, 1998) and the αβ-tubulin heterodimer (Nogales et al., 1998) also show a high degree of similarity. FtsZ self-polymerizes, forms a ring at the equator of the bacterial cell, and determines the division site of the cell (Bi and Lutkenhaus, 1991). Blocking the function of FtsZ or changing the level of FtsZ blocks bacterial cell division and causes long filamentous cells (Dai and Lutkenhaus, 1992; Dewar et al., 1992). FtsZ has different behaviors during the cell cycle: polymerization to a ring (Z ring) at midcell, maintenance of the ring through dynamic subunit turnover, and constriction and disassembly of the Z ring during cell division (Romberg and Levin, 2003; Adams and Errington, 2009).

The polymerization mechanism of FtsZ is also similar to that of tubulin (Scheffers et al., 2002). *In vivo*, Z rings can be assembled within 1 to 3 min and disassembled within 1 min (Sun and Margolin, 1998; Sun et al., 1998). Fluorescence recovery after photobleaching showed that the Z ring is highly dynamic throughout its existence and contains about 30% of cellular FtsZ protein (Stricker et al., 2002). In addition, the FtsZ protein in the Z ring can exchange with FtsZ protein in the cytosol very quickly (Stricker et al., 2002). These characteristics are based on the GTP-dependent, reversible polymerization of FtsZ. GTP is hydrolyzed immediately after FtsZ polymerization, and the FtsZ polymer contains both GDP and inorganic phosphate (Scheffers and Driessen, 2002). Preformed FtsZ polymers can be stabilized by addition of nonhydrolyzable GTP-γ-S with more than 95% of the nucleotide associated with the FtsZ polymer in the GDP form, and be rapidly destabilized by addition of GDP (Scheffers et al., 2000; Mukherjee et al., 2001; Scheffers and Driessen, 2001; Scheffers and Driessen, 2002). These data indicated that, similar to tubulin, phosphate release may also be important for FtsZ polymer dynamics.

Molecular motors like dynein, kinesin or myosin are absent in bacteria. Therefore, the force generation mechanism of the cell division machinery in bacteria seems to be different from that of eukaryotic cells. It has long been conjectured that FtsZ is a force generation protein. This has been confirmed until recently by both model prediction and experimental evidence. Mathematics and physics model predicted that by hydrolyzing GTP and subunit turnover, FtsZ filaments can condense and generate a small constriction force sufficient for bacterial cell division (Lan et al., 2007; Allard and Cytrynbaum, 2009; Erickson, 2009; Lan et al., 2009). A membrane-targeted FtsZ mixed with lipid vesicles can form multiple Z rings and constrict liposomes (Osawa et al., 2008), suggesting FtsZ can generate a force itself without other motor proteins.

In plants, there are at least two classes of FtsZ: FtsZ1 and FtsZ2 (Osteryoung and Vierling, 1995; Osteryoung et al., 1998; Strepp et al., 1998; Stokes et al., 2000; Stokes and Osteryoung, 2003). They can hydrolyze GTP and polymerize into thin protofilaments like bacterial FtsZ (Olson et al., 2010). They are all targeted into chloroplasts by a cleavable transit peptide (McAndrew et al., 2001). The C-terminal core domain is conserved in FtsZ2 but not FtsZ1. Phylogenetic analysis indicates that they are all closely related to cyanobacterial FtsZ (Rensing et al., 2004). Both FtsZ1 and FtsZ2 were shown to be important for chloroplast division and they may have distinct roles in chloroplast division (Schmitz et al., 2009). Antisense suppression, knockout and overexpression of FtsZ1 or FtsZ2 can cause enlarged and fewer chloroplasts in the cell (Osteryoung et al., 1998; Strepp et al., 1998; Stokes et al., 2000; Deena Kadirjan-Kalbach, personal communication). In extreme cases, there is only one chloroplast per cell. FtsZ1 and FtsZ2 were shown to form a ring and colocalize at the division site of chloroplasts by immunofluorescence microscopy and expression of GFP fusion proteins in *A. thaliana* (Mori et al., 2001; Vitha et al., 2001). Even in the antisense and overexpressing FtsZ plants, FtsZ1 and FtsZ2 are still colocalized (McAndrew et al., 2001) (Stan Vitha, personal communication). It was shown that in wild-type plants the molecular ratio between FtsZ1 and FtsZ2 is fixed at 1:2 (McAndrew et al., 2008). Thus, it seems that the correct ratio between the two types of FtsZ is important for their proper function in chloroplast division.

Mitochondria are also derived from bacteria as endosymbionts but at a time earlier than chloroplasts (Dyall et al., 2004). The division machinery of mitochondria seems to be simpler than that of chloroplasts (Osteryoung and Nunnari, 2003). In animals, fungi and higher plants, there is no mitochondrial division protein with a prokaryotic origin (Osteryoung and Nunnari, 2003). However, FtsZ was found in some red algae and protists and shown to be localized to the middle of mitochondria and required for the normal morphology of mitochondria (Beech et al., 2000; Takahara et al., 2000; Gilson et al., 2003; Kiefel et al., 2004). In *Dictyostelium*, two mitochondrial FtsZs, FszA and FszB, were found (Gilson et al., 2003). FszA is localized to the future or recent division sites of mitochondria (Gilson et al., 2003). However, FszB was found in an electron-dense, submitochondrial body usually located at one end of the organelle (Gilson et al., 2003). The evolution of the mitochondrial division machinery seems to be an ongoing process. The mitochondrial FtsZ probably is the last bacteria-derived division protein to be left and it has been lost many times in different species (Kiefel et al., 2004).

Min system

Proper cell division in bacteria requires accurate positioning of the division plane in the middle of the cell, which is

determined by the placement of the FtsZ ring. The site of FtsZ ring assembly is in turn controlled by the *min* (*mini-cell*) operon, which suppresses FtsZ polymerization at sites other than the middle of the cells (de Boer et al., 1989; Lutkenhaus, 2007). MinC, MinD, and MinE are the proteins encoded by the *min* operon, which is conserved in many bacteria including cyanobacteria. The Min proteins in *E. coli*, when expressed at a certain ratio, undergo a highly dynamic localization cycle, during which they oscillate between the membrane of both cell halves, to ensure the proper placement of the cell division site (de Boer et al., 1991; Mulder et al., 1992; Margolin, 2001; Kruse et al., 2007; Lutkenhaus, 2007; Fischer-Friedrich et al., 2010; Ivanov and Mizuuchi, 2010).

MinC and MinD forms a complex to regulate cell division by inhibiting FtsZ polymerization and assembly of the Z ring (Bi and Lutkenhaus, 1993; Lutkenhaus, 2007). A functional MalE-MinC fusion protein was shown to interact with FtsZ and prevent its polymerization without affecting the GTPase activity (Hu et al., 1999). A functional GFP-MinC was shown to oscillate rapidly between the halves of the cell independently of FtsZ (Hu and Lutkenhaus, 1999; Raskin and de Boer, 1999a). However, GFP-MinC is a cytoplasmic protein with no oscillation in the absence of the other Min proteins (Hu and Lutkenhaus, 1999). The addition of MinD, which interacts with MinC, results in the localization of GFP-MinC on the membrane (Hu and Lutkenhaus, 1999; Shiomi and Margolin, 2007). MinD is an ATPase located on the the inner membrane region of the cell envelope (de Boer et al., 1991; Taghbalout et al., 2006). A functional GFP-MinD was also shown to have a rapid oscillation cycle which is imposed by MinE (Raskin and de Boer, 1999b). These results support a model in which MinD recruits MinC to inhibit FtsZ ring formation near the cell ends and force FtsZ assembly in the middle.

In the absence of MinE, MinC and MinD function coordinately and result in blocking of cell division (de Boer et al., 1992b). MinE can reduce the interaction between MinC and MinD (Huang et al., 1996; Ghasriani et al., 2010). MinE directly interacts with the membrane and forms a dynamic ring that undergoes a repetitive cycle of movement first to one cell pole and then to the opposite pole (Fu et al., 2001; Fischer-Friedrich et al., 2010; Hsieh et al., 2010). Taken together with studies of the dynamic behavior of MinCD, the MinE ring represents a cell structure that allows FtsZ ring formation at midcell by suppressing MinCD activity at this site.

To further investigate the molecular basis of the oscillation of the Min system, a series of *in vitro* experiments was done. MinD was shown to bind to phospholipid vesicles in the presence of ATP and to assemble into a well-ordered helical array that forms the vesicles into tubes in a cooperative fashion (Hu et al., 2002; Lackner et al., 2003). MinD can recruit either MinC or MinE in an ATP-dependent manner (Hu et al., 2003). MinE can promote bundling of MinD filaments as well as their disassembly by activating the ATPase activity of MinD (Suefuji and Valluzzi, 2002). MinE stimulates dissociation of MinC from MinD:ATP-membrane complexes even without ATP hydrolysis (Hu et al., 2003; Ghasriani et al., 2010). In contrast, MinC is unable to displace MinE bound to the MinD-bilayer complex (Hu et al., 2003; Lackner et al., 2003). These results suggest that MinE induces conformational changes in membrane-bound MinD, which results in the release of MinC and then the conversion of membrane-bound MinD (MinD:ATP) to cytoplasmic MinD (MinD:ADP).

In some green algae, such as *Chlorella vulgaris*, *minD* and *minE* genes are present in the chloroplast genome and arranged in the same order as in *E. coli* (Wakasugi et al., 1997). In higher plants, these two genes are present in the nuclear genome and the gene products are targeted to chloroplasts by an N-terminal transit peptides (Colletti et al., 2000; Dinkins et al., 2001; Itoh et al., 2001; Maple et al., 2002; Reddy et al., 2002; Fujiwara et al., 2004). Antisense repression of *MinD* expression in transgenic *Arabidopsis* plants causes a phenotype of asymmetric chloroplast division and highly variable chloroplast size, suggesting a misplacement of the chloroplast division machinery (Colletti et al., 2000). Overexpression of *AtMinD* also inhibits chloroplast division in both *Arabidopsis* and tobacco (Colletti et al., 2000; Dinkins et al., 2001). Immuno-staining of FtsZ in plants overexpressing *MinD* shows random and short FtsZ filaments throughout the giant chloroplast, while parallel FtsZ rings are distributed ectopically at multiple sites along the enlarged chloroplast in the antisense *MinD* transgenic plants (Vitha et al., 2003). Giant chloroplasts were also observed in transgenic plants with higher or lower expression levels of *MinE* (Itoh et al., 2001; Maple et al., 2002; Reddy et al., 2002). Specifically, in the plants overexpressing *AtMinE*, the chloroplast division sites were misplaced, giving rise to either asymmetric or multiple constrictions along the length of chloroplasts (Maple et al., 2002). The phenotypes observed in *minD* and *minE* mutant plants resemble those of bacterial mutants with altered *minD* and *minE* expression levels (Fujiwara et al., 2008), suggesting that their working mechanisms may be similar.

Based on BLAST searches of the genome sequences of *Arabidopsis*, rice and *Chlamydomonas* and of the EST data from many plant species, *MinC* is missing in plants. According to the model of the Min system in bacteria, MinC is the protein that directly prevents FtsZ ring formation at non-mid-cell sites. Therefore, plants must have a protein with a role similar to that of MinC in order to allow the Min system to function in chloroplasts. One possibility is that the role of MinC is taken by another protein. In *Bacillus subtilis*, MinE is missing and its role probably is taken by DivIVA (Cha and Stewart, 1997; Howard, 2004), supporting this hypothesis. Alternatively, MinC is present in plants and the reason it has not been discovered is that its sequence is not well conserved. This is supported by the fact that all known cyanobacterial species have MinC, MinD and MinE but that

protein sequences of MinC are much less conserved than those of MinD, MinE and many other cell division proteins. Still, the function of MinC may be well conserved. Overexpression of a chloroplast-targeted *E. coli* MinC in plants resulted in an inhibition of chloroplast division (Tavva et al., 2006). To find the MinC homolog in plants, approaches other than BLAST search, such as search based on protein structure, may be more useful.

FTN2 and ARC6

Ftn2 is a cell division gene conserved only in cyanobacteria but not in other bacteria (Koksharova and Wolk, 2002). A transposon insertion in the *Ftn2* gene in *Synechococcus* sp. strain PCC 7942 blocks cell division. The mutant cells are up to 100-fold longer than wild-type cells and their colonies show an irregular spreading phenotype (Koksharova and Wolk, 2002). FTN2 has a domain of DnaJ cochaperones at its N terminus and interacts with FtsZ in a bacterial two-hybrid system (Koksharova and Wolk, 2002; Mazouni et al., 2004). *In vitro* experiments with the purified proteins showed that FTN2 can also decorate the FtsZ filaments and that the DnaJ domain is critical for the decoration (Mazouni et al., 2004).

arc6 is a chloroplast division mutant in *Arabidopsis* with only one or two chloroplasts per cell (Pyke et al., 1994; Marrison et al., 1999). The *arc6* locus was mapped to a region containing the *Ftn2* homolog (Marrison et al., 1999). Sequencing of this gene revealed a nonsense mutation (Vitha et al., 2003). Complementation of the mutant phenotype by the wild-type gene confirmed that *ARC6* is the *Ftn2* homolog in plants (Vitha et al., 2003). Chloroplasts in the *arc6* mutant contain numerous short, disorganized FtsZ filament fragments. *arc6* plants have a reduced level of FtsZ proteins but a normal level of *FtsZ* mRNA, indicating that their FtsZ proteins are less stable than that in wild type. A functional ARC6-GFP was shown to be localized to a ring at the center of the chloroplasts.

The data from Ftn2 in cyanobacteria and ARC6 in plants suggest that they may function similarly in stabilizing the constricting FtsZ ring.

SulA

SulA, which is induced as part of the DNA-damage response (Huisman et al., 1980), inhibits bacterial cell division by interacting with FtsZ and preventing its polymerization (Mukherjee et al., 1998; Trusca et al., 1998; Dajkovic et al., 2008). In *sulA* and *sulB* mutants, cell division is not blocked after DNA-damaging treatments as in wild type (Jones and Holland, 1985). Induction of the expression of the wild-type *sulA* gene with the *lac* promoter by IPTG is sufficient to cause inhibition of cell division (Huisman et al., 1984). This inhibition can be suppressed by mutations in the s*ulB* gene if *sulA* is not highly expressed (Huisman et al., 1984). Cloning of the *sulB* gene indicated that it encodes FtsZ (Jones and Holland, 1985). In the absence of FtsZ or in the *sulB114* mutant, SulA is extremely unstable with a half-life of only 3 min, in contrast to its normal half life of 12 min in the presence of FtsZ (Jones and Holland, 1985). These data suggest that SulA interacts directly with FtsZ *in vivo* to block cell division. In the presence of GTP and Mg^{2+}, SulA protein was shown to interact with FtsZ and form a stable complex in a molar ratio of approximately one to one (Higashitani et al., 1995). The role of GTP cannot be replaced by GDP or GTP-γ-S, suggesting that hydrolysis of GTP is required for the interaction between SulA and FtsZ (Higashitani et al., 1995). SulA inhibits the polymerization of FtsZ but not the polymerization of purified SulB mutant protein (Mukherjee et al., 1998; Trusca et al., 1998). By alanine-scanning mutagenesis, the central region of SulA was shown to be essential for the FtsZ polymerization inhibition (Higashitani et al., 1997). By using deletion mutants, residues 3–27 and the 21 residues at the C-terminal end were shown not to be required for the inhibition, while the mutant protein lacking N-terminal residues 3–47 or 34 residues at the C-terminal end was inactive (Higashitani et al., 1997). SulA forms into a dimer either alone or in complex with FtsZ (Cordell et al., 2003). SulA inhibits FtsZ polymerization and cell division by binding to the T7 loop surface of FtsZ (opposite to the nucleotide binding site) without inducing conformational change (Cordell et al., 2003; Dajkovic et al., 2008).

Homologs of SulA are also found in plants and play a role in chloroplast division (Maple et al., 2004; Raynaud et al., 2004). The gene product of *AtSulA* is predicted to be targeted to the chloroplast. The expression pattern of *AtSulA* is similar to that of other chloroplast division genes, such as *FtsZ*s, *MinD* and *MinE*. In transgenic plants, AtSulA-GFP protein is imported into chloroplasts and the overexpression of *AtSulA* inhibits chloroplast division in various cell types. Overexpression of *AtSulA* can overcome the chloroplast division defect caused by overexpresion of *FtsZ*. Since the formation of too many FtsZ polymers can block chloroplast division, these data suggest that SulA in plants functions similarly to SulA in bacteria by preventing FtsZ polymerization.

Innovations in the chloroplast division machinery during evolution

The endosymbiotic origin of chloroplasts occurred more than one billon years ago. Since then, chloroplasts have experienced great changes in the long history of evolution and acquired new protein components to function as an organelle in modern plants (Dyall et al., 2004). For example, chloroplasts have evolved protein import machinery complexes to import thousands of proteins encoded by the nuclear genome (Reumann et al., 1999; Gross and Bhattacharya, 2009). Cyanobacteria have a cell wall between the inner and outer membrane, but there is no cell wall between the inner and outer envelope of chloroplasts and the outer envelope of

chloroplasts has acquired many eukaryotic properties (Douce and Joyard, 1990; Dyall et al., 2004; Vesteg et al., 2009). Moreover, the division of chloroplasts must be under control of the host cells. Therefore, new components of the chloroplast division machinery must have evolved to adapt to the environment in host cells.

FtsZ1

In cyanobacteria, there is only one type of FtsZ. However, there are two types of FtsZ in plants: FtsZ1 and FtsZ2 (Osteryoung and McAndrew, 2001). FtsZ1 and FtsZ2 are closely related and very similar to the FtsZs in cyanobacteria (Osteryoung and McAndrew, 2001). FtsZs in most bacteria have a conserved N-terminal GTPase domain, C-terminal domain and the C-terminal core domain (Lowe and Amos, 1998; Mosyak et al., 2000). The C-terminal core domain at the extreme end contains a highly conserved sequence motif, D/E-I/V-P-X-F/Y-L, which is required for direct interactions between FtsZ and two other essential cell division proteins, ZipA and FtsA (Mosyak et al., 2000; Yan et al., 2000). All three domains are conserved in FtsZ2 (Osteryoung and McAndrew, 2001). However, the C-terminal core domain is not present in FtsZ1 of plants (Osteryoung and McAndrew, 2001; Schmitz et al., 2009; Olson et al., 2010). Similar to FtsZ2, suppression of FtsZ1 expression or overexpression of FtsZ1 causes severe division phenotypes, suggesting that FtsZ1 and FtsZ2 are both essential for chloroplast division, but they may have different roles (Osteryoung et al., 1998; Stokes et al., 2000; Schmitz et al., 2009). Phylogenetic analysis indicates that FtsZ1 and FtsZ2 may have diverged at the very early stages of plant evolution, further supporting the distinct role of FtsZ1 in the evolution of the chloroplast division machinery (Stokes and Osteryoung, 2003; Rensing et al., 2004).

There are several possible explanations for the role of FtsZ1 in chloroplast division. First, the appearance of FtsZ1 during evolution may provide spacers for FtsZ proteins to form a ring suitable for chloroplasts. Since the diameter of bacterial cells is typically ~1 μm and the diameter of chloroplasts is typically 4–8 μm (Osteryoung et al., 1998; Koksharova and Wolk, 2002), one can envision that if there is only FtsZ2 in plants, there may be topological hindrances for FtsZ2 proteins to form a ring as large as required for chloroplast division. Second, the C-terminal end of FtsZ1 may have acquired new functions for the regulation of its activity. The third possibility is that the role of FtsZ1 is to provide enough proteins to be assembled into a ring together with FtsZ2 in chloroplasts and their functions are redundant. This seems to be less likely and has been tested by replacing *FtsZ1* with *FtsZ2* (Schmitz et al., 2009). In the *FtsZ1* knockout plants, a transgene of *FtsZ2* cannot rescue the mutant phenotype, and vice versa. Recently, it was shown that FtsZ1 can coassembly with FtsZ2 into bundled protofilaments and promote lateral interactions between protofilaments (Olson et al., 2010). This could be another explanation.

ARC3

arc3 is a chloroplast division mutant in *Arabidopsis* with 10–20 chloroplasts per cell (Pyke and Leech, 1994; Marrison et al., 1999). Cloning of *ARC3* indicated that it encodes an FtsZ-like protein and the *arc3* mutant is a null allele (Shimada et al., 2004). The N terminus of ARC3 shares low similarity with the GTPase domains of FtsZ1 and FtsZ2. The C terminus of ARC3 has a membrane-occupation-and-recognition-nexus (MORN) repeat motif similar to that of phosphatidylinositol-4-phosphate 5-kinases (PIP5K) (Shimada et al., 2004). ARC3 was shown to be localized to a ring to the chloroplast division site (Shimada et al., 2004; Maple et al., 2007). ARC3 interacts specifically with FtsZ1 and belongs to an FtsZ1-FtsZ2-ARC3-ARC6 complex (Maple et al., 2007; McAndrew et al., 2008). Because many residues essential for the GTPase activity in FtsZ are not conserved in ARC3 (Osteryoung and McAndrew, 2001; Shimada et al., 2004), this protein may not have GTPase activity and its function might be quite different from that of FtsZ1 and FtsZ2. Since chloroplast division is still occurring in the null alleles of the *arc3* mutant (Pyke and Leech, 1994; Marrison et al., 1999; Shimada et al., 2004), ARC3 may have evolved to modify the chloroplast division machinery.

ARC6H/PARC6/CDP1

ARC6H, PARC6 and CDP1 all refer to the same protein, At3G19180, which is a homolog of ARC6 and originated in higher plants. Mutations in this gene cause a severe chloroplast division phenotype (Glynn et al., 2009; Zhang et al., 2009; Eric Ottesen and Gayle, 2010). Chloroplasts in bundle sheath cells of the mutant plant showed a phenotype of multiple constriction sites and parallel FtsZ rings. This is similar to that of *minD* and *arc3* mutant (Pyke and Leech, 1994; Colletti et al., 2000; Shimada et al., 2004) and suggests a close relation of the function of these proteins. Yeast two-hybrid analysis indicated that At3G19180 interacts with ARC3 (Glynn et al., 2009; Zhang et al., 2009). Similar to that of ARC3, a GFP fusion protein of At3G19180 was localized to the chloroplast division site or single spots at one pole (Glynn et al., 2009). Further biochemical analysis indicated that At3G19180 is a membrane protein localized to the inner envelope of chloroplasts. Thus, At3G19180 is a novel component of the chloroplast division site positioning system and its function is different from its homolog ARC6, which is required for the stability of FtsZ rings (Vitha et al., 2003).

MCD1

MCD1 probably is an invention of land plants for chloroplast division. In *mcd1* mutants, multiple chloroplast division sites and FtsZ rings were observed as in *minD* and *arc3* mutants

(Pyke and Leech, 1994; Vitha et al., 2003), suggesting a defect in the correct placement of the division site to the middle of chloroplasts (Nakanishi et al., 2009). MCD1 was shown to be an inner membrane protein with its C-terminal part interacting with MinD (Nakanishi et al., 2009). The proper localization of MinD is also MCD1-dependent. Thus, MCD1 is another novel component of the chloroplast division site positioning system in plants.

ARC5

arc5 is a chloroplast division mutant in *Arabidopsis* with 1–15 enlarged dumbbell-shaped chloroplasts per cell (Pyke and Leech, 1994; Robertson et al., 1996; Marrison et al., 1999; Gao et al., 2003). The phenotype of *arc5* indicated that the *ARC5* gene product may be involved in the constriction of chloroplasts during division (Pyke and Leech, 1994; Robertson et al., 1996; Marrison et al., 1999; Gao et al., 2003). *ARC5* is the first chloroplast division gene identified by positional cloning (Gao et al., 2003). A *GFP-ARC5* fusion gene rescues the *arc5* mutant phenotype and the gene product is localized to a ring at the chloroplast division site. Chloroplast import and protease protection assays indicate that the ARC5 ring is positioned on the outer surface of the chloroplast (Gao et al., 2003). Similar results have also been observed for the homolog of ARC5 in a red alga (Miyagishima et al., 2003). Thus, ARC5 is the first cytosolic component of the chloroplast division complex to be identified. ARC5 is related to a group of dynamin-like proteins shown to be unique to plants by phylogenetic analysis (Gao et al., 2003; Miyagishima et al., 2003). It has no obvious counterparts in prokaryotes, suggesting that it evolved from a dynamin-related protein present in the eukaryotic ancestor of plants.

Dynamin and its relatives are large GTPases that participate in a variety of organellar fission and fusion events in eukaryotes, including budding of endocytic and Golgi-derived vesicles, mitochondrial fission, mitochondrial fusion, and plant cell plate formation (Chen et al., 1991; Wilsbach and Payne, 1993; Gu and Verma, 1996; Pelloquin et al., 1998; Bleazard et al., 1999; Sesaki and Jensen, 1999; Praefcke and McMahon, 2004). Structural analysis of dynamin indicates that it spontaneously self-assembles into rings and stacks of interconnected rings (Hinshaw and Schmid, 1995; Kelly, 1995; Carr and Hinshaw, 1997; Low and Lowe, 2010). Purified recombinant dynamin binds to a lipid bilayer in a regular pattern to form helical tubes that constrict and vesiculate upon GTP addition (Sweitzer and Hinshaw, 1998; Takei et al., 1998; Kuroiwa et al., 2008). In the *shibire* mutant of *Drosophila*, which has a mutation in the *dynamin-1* gene, many pit-like structures were observed to accumulate on the plasma membrane near presynaptic sites (Kosaka and Ikeda, 1983a, 1983b). A 10-nm-thick electron-dense ring, reminiscent of a "collar", was observed at the neck part of those pit-like structures (Kosaka and Ikeda, 1983a). In GTP-γ-S-treated nerve terminals, tubular invaginations of the plasma membrane were surrounded by transverse electron-dense rings that were positive for dynamin immunoreactivity (Takei et al., 1995). These results, in addition to the finding that dynamin is capable of generating force, strongly support the hypothesis that dynamin is active in the fission reaction (Sweitzer and Hinshaw, 1998). Thus, it was suggested that dynamin is a mechanoenzyme directly involved in membrane remodeling when the vesicles are pinched off.

Most of the dynamin-related proteins have four conserved domains: a GTPase domain, a middle domain, a Pleckstrin homology (PH) domain and a GTPase effector domain (GED) (Hinshaw, 2000; Praefcke and McMahon, 2004; Low and Lowe, 2010). Dynamin is proposed to be a mechano-enzyme and its GTPase activity may be involved in the generation of force (Warnock and Schmid, 1996; Sweitzer and Hinshaw, 1998). The middle domain is involved in protein–protein interactions between dynamin molecules and is also essential for the function of dynamin (Smirnova et al., 1999; Ramachandran et al., 2007). The PH domain is involved in the specific membrane binding of dynamin (Salim et al., 1996; Zheng et al., 1996; Ramachandran et al., 2009). The GED domain interacts with the GTPase domain and modifies its activity (Fukushima et al., 2001; Chugh et al., 2006). ARC5 is relatively more divergent from dynamin than other dynamin-related proteins (Gao et al., 2003). The GTPase domain and the middle domain of ARC5 can be aligned with other dynamin-related proteins better than can the PH and GED domains (Gao et al., 2003). ARC5 may therefore generate force to facilitate chloroplast division, but it functions at a site quite different from those of other dynamin-related proteins, and the diameter of the ARC5 ring is much larger than the diameter of the rings formed by other dynamin-related proteins. These results indicate that the chloroplast division machinery is of mixed evolutionary origin and that it shares structural and mechanistic similarities with both the cell division machinery of bacteria and the dynamin-mediated organellar fission machineries of eukaryotes.

PDV1 and PDV2

PDV1 was discovered by mutant screening and map-based cloning (Miyagishima et al., 2006). The phenotype of *pdv1* mutant is similar to that of *arc5* mutant, suggesting that their functions might be related. Topological analysis suggested that PDV1 is a chloroplast outer envelope protein with a predicted coiled-coil domain in the cytosol and a C-terminal part in the intermembrane space. GFP-PDV1 was localized to chloroplast division site with a discontinuous pattern, similar to that of GFP-ARC5 (Miyagishima et al., 2006).

PDV2 is homologous to PDV1 with similar gene structure and protein topology (Miyagishima et al., 2006). The phenotype of *pdv2* mutant is similar to that of *pdv1* and *arc5* mutant, suggesting their functions are related too.

However, GFP-PDV2 was localized to a continuous ring at the chloroplast division site (Glynn et al., 2008). Further experiments indicated that the C-terminal region of ARC6 interact with the C-terminal region of PDV2 in the intermembrane space, but not that of PDV1 (Glynn et al., 2008). This may explain why the localization pattern of PDV2 is similar to that of ARC6, not PDV1. The interaction between PDV2 and ARC6 links the chloroplast division machinery from the cytosol to the stroma.

Localization of ARC5 was affected in *pdv1*/*pdv2* double mutant (Miyagishima et al., 2006). Therefore, they seem to be required for the proper localization of ARC5. Evidence of the direct interaction between PDV1/PDV2 and ARC5 is lacking. It is unclear whether they recruit ARC5 to the chloroplast division site or not. PDV1 and PDV2 were only found in land plants. Because their sequences are not highly conserved across different species, it is unclear whether there is any homolog of PDV1 and PDV2 in algae, or they are not required for lower plants.

Components that were probably lost or replaced by others during evolution

Since chloroplasts lost their autonomy during their evolution, some of the bacterial functions are apparently no longer important for chloroplast function and the associated genes were lost. For example, nitrogen fixation is important for the survival of cyanobacteria but not important for the function of chloroplasts, so that many of the genes for nitrogen fixation were lost in evolution. This may also be partly true for chloroplast division genes. The morphology of plant chloroplasts is somewhat different from that of cyanobacteria. It is not surprising that some of the cell division proteins found in cyanobacteria are not conserved in plants. FtsA, Ftn6, FtsI and FtsW may be examples.

FtsA and MreB

FtsA belongs to a superfamily of ATPases that includes FtsA, DnaK, HSP70, ParM, MreB, actin and hexokinase (Bork et al., 1992; Lowe et al., 2004). They all have similar structures and ParM and MreB have been shown to form filaments structurally similar to actin filments (van den Ent et al., 2002; Carballido-Lopez, 2006). FtsA, DnaK, HSP70 and MreB are also very similar in sequence and may be homologs in different species with at least partially similar functions (Amos et al., 2004; Lowe et al., 2004; Marbouty et al., 2009). Sometimes, they may have the same function but have been annotated with different names in different species. This kind of confusion may be due to conservation and variations among these proteins but also to the fact that they were studied in different species from different perspectives. Here we will focus on FtsA and MreB, which function respectively in bacterial cell division and shape determination, and HSP70s, the homologs of cyanobacterial FtsA or MreB in plants.

FtsA was initially found by an *fts* screen (Wijsman and Koopman, 1976). FtsA is a bacterial cell division protein localized to a ring at the division site (Ma et al., 1996); Its localization depends on FtsZ, whereas FtsZ's localization does not depend on FtsA (Addinall and Lutkenhaus, 1996). FtsA binds to the membrane and interacts with the C-terminal core domain of FtsZ (Pichoff and Lutkenhaus, 2005, 2007). In some *ftsZ* mutants with mutations in the coding region of the C-terminal core domain, FtsZ can form a ring but cannot recruit FstA (Ma and Margolin, 1999). In the absence of FtsA, several other cell division proteins cannot be localized to the division site (Errington et al., 2003; Rico et al., 2004). FtsA can be phosphorylated and bind ATP, but this seems to be not essential for its function (Sanchez et al., 1994). The molecular ratio between FtsA and FtsZ in *E. coli* is 1:100 (Dai and Lutkenhaus, 1992; Dewar et al., 1992). Alteration of this ratio will affect cell division.

MreB regulates the rod shape of bacterial cells in *Bacillus subtilis* and many other species and is believed to be the prokaryotic form actin (Jones et al., 2001; van den Ent et al., 2001a; Graumann, 2007). MreB forms helical filamentous structures that surround the periphery of the cell, presumably just under the cytoplasmic membrane, and increases the mechanical stiffness of the cell (Egelman, 2003; Wang et al., 2010). Knocking out of MreB in rod-shaped bacteria results in a spherical morphology (Jones et al., 2001). *In vitro*, MreB can assemble into two-stranded protofilaments with a subunit repeat similar to that of F-actin, except that the strands do not twist around each other (van den Ent et al., 2001a; van den Ent et al., 2001b; Popp et al., 2010). The crystal structure of MreB shows that its folding is also very similar to that of actin, except that there are insertions in actin (van den Ent et al., 2001a; van den Ent et al., 2001b). These insertions are important for the allosteric interactions within the actin subunit, subunit-subunit interactions in the filament, and interactions with other proteins.

Homologs of MreB or FtsA are also present in cyanobacteria and plants. The role of MreB or FtsA homologs in cyanobacteria is unknown. However, their homologs in plants are called HSP70. There are multiple copies of *HSP70* genes related to chloroplast function. In plant cells, when proteins are imported into chloroplasts, the HSP70s on the cytosolic side of the chloroplast import machinery may help to recognize the chloroplast transit peptide and unfold the proteins, HSP70s in the intermembrane space may be required for the translocation of chloroplast-targeted proteins, and the HSP70s on the stromal side may help the translocation and refolding of the proteins (Gray and Row, 1995; Jackson-Constan et al., 2001; Jarvis and Soll, 2002). Based on expressed sequence tag (EST) data, the mRNAs of these *HSP70* genes are much more abundant than those of *FtsZ* genes, in great contrast to the molecular ratio between FtsA and FtsZ in bacteria. Also, chloroplasts mostly have a spherical shape, similar to the bacteria that lack MreB. Thus,

the homologs of FtsA or MreB in plants, chloroplast-targeted HSP70s, may not have a role in chloroplast division or morphology.

Ftn6

Ftn6 is a cyanobacteria-specific cell division protein. Knockout of *Ftn6* either by transposon insertion or homologous recombination affects cell division in *Synechococcus* sp. strain PCC 7942 and *Anabaena* sp. strain PCC 7120 (Koksharova and Wolk, 2002). The function of Ftn6 is unknown and there is no homolog of Ftn6 in other bacteria. Since not all the known cell division proteins in *E. coli* are found to have homologs in cyanobacteria and vice versa, Ftn6 may either have a role similar to some division proteins in *E. coli* or have a role unique to cyanobacterial cell division. The phenotype of *ftn*6 mutants is not as severe as that of *ftn*2 mutants (Koksharova and Wolk, 2002) and the protein sequences of Ftn6 are not well conserved in different cynaobacteria species. There is also no homolog of Ftn6 in plants, suggesting that the function of Ftn6 is not important for chloroplast division and that Ftn6 was lost during chloroplast evolution.

FtsI

FtsI, also called penicillin binding protein 3 (PBP3), is a transpeptidase required for cross-linking of the peptidoglycan cell wall at the bacteria cell division site (Nakamura et al., 1983; Weiss et al., 1997). FtsI is conserved in many bacteria including cyanobacteria (Margolin, 2000). It has a small cytoplasmic domain, a transmembrane domain, a domain of unknown function, and a transpeptidase domain (Wissel and Weiss, 2004). The last two domains reside in the periplasm (Wissel and Weiss, 2004). Immuno-staining and a functional GFP fusion protein indicated that FtsI is localized to the cell division site (Weiss et al., 1997; Weiss et al., 1999). Inhibition of the catalytic activity of FtsI blocks bacteria cell division but does not affect the localization of FtsI (Pogliano et al., 1997; Weiss et al., 1999). Localization of FtsI to the division site requires its membrane anchor, FtsZ, FtsW, FtsA, FtsQ, and FtsL (Weiss et al., 1999; Mercer and Weiss, 2002). It was suggested that the interaction with other division proteins can stimulate the catalytic activity of PBP3 (Eberhardt et al., 2003). GFP-FtsI is localized to the division site during the later stages of cell growth and throughout the process of division (Weiss et al., 1999). Once FtsI is inactivated, FtsZ ring stays at the midpoint of the cell and its constriction is severely affected (Pogliano et al., 1997). These data suggest that FtsI functions in the late stage of cell division.

Unlike cyanobacteria, peptidoglycan wall was not found in the chloroplast intermembrane space (Machida et al., 2006). However, penicillin can inhibit chloroplast division in the moss *Physcomitrella patens* (Kasten and Reski, 1997; Katayama et al., 2003). This phenomenon is not observed in seed plants, such as tomato and *Arabidopsis* (Kasten and Reski, 1997). With the sequenced genome of moss (Rensing et al., 2008), genes for peptidoglycan biosynthesis pathway were discovered (Takano and Takechi, 2010). Knockout of *PpPbp*, *PpMurE*, *PpMurA* and *PpMraY* genes all showed a phenotype of enlarged chloroplasts (Machida et al., 2006; Homi et al., 2009), suggesting a role of chloroplast division of these genes. It needs to be further investigated whether the chloroplast in moss really has a peptidoglycan wall and whether this wall is related to chloroplast division if it does exist. In the sequenced genomes of *Arabidopsis*, rice and many other higher plants, no FtsI homolog has been found. This indicates that FtsI probably was lost during evolution in higher land plants. The *Arabidopsis* genome has five homologs of Mur genes (Machida et al., 2006). However, they seem to be not involved in chloroplast division (Garcia et al., 2008). It will be interesting to learn how higher plants can overcome the loss of peptidoglycan biosynthesis genes which are important for chloroplast division in moss.

FtsW

FtsW is an essential bacterial cell division protein with 10 transmembrane domains and a large periplasmic loop (Ishino et al., 1989; Lara and Ayala, 2002). Both the N- and the C-terminus of FtsW are located in the cytoplasm (Lara and Ayala, 2002). FtsW is also well conserved in cyanobacteria (Margolin, 2000). Although the sequence of FtsW is somewhat similar to that of the bacterial cell shape-determining protein RodA, mutations in FtsW only affect cell division and not cell shape (Khattar et al., 1994). FtsW is localized to the division site and interacts with FtsZ through its C-terminal tail (Datta et al., 2002). In the absence of FtsW, the formation of the FtsZ ring is affected, indicating that FtsW may have a role similar to that of another membrane protein, ZipA, in stabilizing FtsZ filaments. FtsW interacts with FtsI and is required for the localization of FstI to the cell division site (Mercer and Weiss, 2002; Fraipont et al., 2011). Thus, FtsW may link FtsZ ring formation in the cytoplasm to peptidoglycan synthesis in the periplasm at the bacteria cell division site.

Neither FtsW nor RodA was found to have a homolog in *Arabidopsis* or rice. Since there is no FtsI in higher plants, FtsW may not be required to be conserved for the localization FtsI. Moreover, the homolog of Ftn2, ARC6, is conserved in plants (Vitha et al., 2003). ARC6 has a transmembrane domain, its N-terminus is located in the stroma, and its C-terminus is located in the intermembrane space. ARC6 is also proposed to have a role in stabilizing FtsZ filaments at the chloroplast division site (Vitha et al., 2003) possibly replacing the function of FtsW.

Conclusion

The last two decades have seen a rapid growth of the knowledge in the areas of bacterial cell division and

chloroplast division. The identification of many bacterial cell division proteins and chloroplast division proteins indicates that the evolution of the chloroplast division machinery has involved both conservation and innovation.

FtsZ probably is the most important division protein for both bacteria and chloroplasts. FtsZ polymerizes and forms a ring at the division site. The FtsZ ring serves as a scaffold for the localization of many other division proteins and generates a force to drive the division (Osawa et al., 2008; Allard and Cytrynbaum, 2009; Lan et al., 2009). The Min system regulates the localization of the FtsZ ring to the mid-cell or mid-chloroplast (Colletti et al., 2000; Itoh et al., 2001; Lutkenhaus, 2002). SulA inhibits the assembly of FtsZ as part of the SOS system in bacteria (Lowe et al., 2004) and its homolog in plants also has a role in chloroplast division (Maple et al., 2004; Raynaud et al., 2004). Ftn2 is a cyanobacteria-specific cell division protein with a DnaJ domain (Koksharova and Wolk, 2002); it is also conserved in plants (Vitha et al., 2003). On the other hand, many bacteria cell division proteins may have been lost during evolution as chloroplasts evolved from bacteria to organelles. During the evolution of plants, new components of chloroplast division machinery, such as ARC5, ARC3, ARC6H, PDV1/2 and MCD1 etc., were also invented at different time points, probably to adapt the change of the properties of chloroplasts or the environment (Gao et al., 2003; Shimada et al., 2004; Miyagishima et al., 2006; Glynn et al., 2009; Nakanishi et al., 2009; Zhang et al., 2009).

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