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REVIEW

Emerging facets of plastid division regulation

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Abstract Plastids are complex organelles that are integrated into the plant host cell where they differentiate and divide in tune with plant differentiation and development. In line with their prokaryotic origin, plastid division involves both evolutionary conserved proteins and proteins of eukaryotic origin where the host has acquired control over the process. The plastid division apparatus is spatially separated between the stromal and the cytosolic space but where clear coordination mechanisms exist between the two machineries. Our knowledge of the plastid division process has increased dramatically during the past decade and recent findings have not only shed light on plastid division enzymology and the formation of plastid division complexes but also on the integration of the division process into a multicellular context. This review summarises our current knowledge of plastid division with an emphasis on biochemical features, the functional assembly of protein complexes and regulatory features of the overall process.

Keywords Plastid division · Protein complexes · Regulation

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Abbreviations

FtsZ	Filamentous temperature sensitive Z
ARC	Accumulation and Replication of Chloroplasts
GC1	Giant Chloroplast 1
MCD1	Multiple Chloroplast Division 1
AtCDP1	Chloroplast Division site Positioning 1
PDV1 and 2	PLASTID DIVISION 1 and 2
CRL	CRUMPLED LEAF
clmp1	Clumped chloroplasts 1
KASI	β-Ketoacyl-[acyl carrier protein] synthase I
CAA33	Constitutive Activator of AAA-ATPase
CJD1	Chloroplast J-like Domain 1

Introduction

Plants and algae contain plastids, essential organelles embedded within the cytoplasmic matrix that are vital for growth and development. Plastids derive from undifferentiated proplastids in meristematic cells, and during cell differentiation proplastids develop into a spectrum of plastid types depending on the developmental state of the cell type in which they reside (Pyke 1997, 1999). Chloroplasts often receive most attention, mainly not only due to their photosynthetic activity, but also due to their involvement in amino acid and fatty acid synthesis as well as their capacity in reducing nitrite to ammonia (Tetlow et al. 2004). Although chloroplasts represent an important plastid category, other plastid types are involved in intermediate metabolic pathways and also act as storage compartments for a variety of compounds. For example, leucoplasts found in petals perform monoterpene synthesis, fruit and flower chromoplasts synthesize and store pigments, amyloplasts in tubers store starch whilst fat is stored in elaioplasts (Tetlow et al. 2004; Waters and Pyke 2005). Given the array of

cellular processes involving plastids in different cell types, it is reasonable to assume that plastid numbers must be maintained and regulated at high stringency throughout the dynamic process of plant differentiation and development.

Based on the endosymbiotic theory plastids arose approximately 1 billion years ago when a eukaryotic cell engulfed a free-living photosynthetic prokaryotic organism (McFadden 1999; Chan et al. 2011). During the endosymbiotic process there was a need not only for the symbiont to replicate to allow for stable maintenance within the eukaryotic cell but also for the host to exert control and regulation over its new acquisition. Because of their prokaryotic ancestry, plastids have retained features of the prokaryotic cell division apparatus but the division process has also clearly had a need to evolve in order to adapt to the partnership. Notably, plastids have not only lost extensive genomic regions but have also transferred numerous genes to the host nucleus. This in effect means that all primary stromal division components have to be imported from the cytosol to their original site of action, a process controlled mainly by the host (Bédard and Jarvis 2005). Most plastids have also acquired a double-membrane structure and lost their peptidoglycan cell wall invoking additional challenges (Cavalier-Smith 2000; Inoue 2011). Further, the host has imposed plant-derived components onto the division process which was most probably a regulatory necessity to fully integrate the symbiont into the multicellular eukaryotic plant body.

The successful division of plastids requires a complex string of temporal and spatial events (Maple and Møller 2010; Miyagishima et al. 2011; Miyagishima 2011). First, proteins involved in the division process have to be translated on cytosolic ribosomes. Second, a subset of division proteins has to be retained in the cytosol whilst others need to be imported into the plastid stroma. Third, the cytosolic and the imported proteins assemble into functional complexes. Fourth, the stromal and cytosolic division machineries have to synchronize their activities to ensure appropriate division. Superimposed onto this complexity is the need for coordination with other plant processes and in particular cell division. As a cell divides it is vital that each new daughter cell retains a certain complement of plastids. This is particularly important in unicellular algae, harbouring a single plastid, where any miscoordination may lead to progeny lacking the organelle. Although most cells in higher plants contain numerous plastids, coordination of organelle and cell division is still required particularly in light of the different cell types created during differentiation.

As the field of plastid division research matures it is becoming evident that the division process is not only highly complex in its own right but also as part of overall plant growth and differentiation. It is often tempting to envisage plastid division as a semi-isolated process, perhaps due to its free-living prokaryotic origin; however, as photosynthetic eukaryotes have evolved, so have the intricacies of the division process and the integration into a multicellular existence. Indeed, little is known how plastid division is influenced by endogenous cues during cellular differentiation, to what extent plastid biogenesis and division are interlinked and moreover how aspects of the division process is specifically controlled and regulated. During the past decade a number of plastid division components have been isolated, characterised and assembled into protein complexes (Table 1; Maple and Møller 2007; Miyagishima et al. 2011; Miyagishima 2011); however, reports describing new *bone fide* division components are becoming less frequent. Perhaps most of the primary division players have now been identified and that it is timely to expand the horizon by overlaying our current plastid division knowledge onto other aspects of plant differentiation and development. This may unravel other mechanisms and pathways involved in the division process and shed light on regulatory aspects. This review will summarise our current knowledge of plastid division by assembling the division components into higher ordered, biochemically active structures with attention to possible regulatory circuits and the overall incorporation into a multicellular and photosynthetic environment.

Biochemical characteristics of plastid division components

The plastid division machinery is represented by what to date appears to be a mixture of structural and biochemically active components. This is perhaps not surprising considering that plastid division requires not only the correct assembly of division components at the appropriate intraplastidic localization but also protein movement and contractile force for membrane constriction (Osawa et al. 2008). Recent studies have added to our increased understanding of the biochemical properties of several plastid division proteins and how this relates to their mode of action.

As in bacteria the FtsZ (filamentous temperature sensitive Z) proteins are commonly viewed as the most central components of the plastid division machinery. Indeed, FtsZ represents the most conserved protein identified to date involved in both cell and organelle division (Ma et al. 1996; Bramhill 1997; Lutkenhaus and Addinall 1997; Rothfield and Justice 1997; Margolin 2000; Addinall and Holland 2002; Romberg and Levin 2003). FtsZ proteins are tubulin-like, self-activating GTPases that are capable of self-assembly forming the Z-ring on the stromal side of the division site (Maple et al. 2005; Olson et al. 2010). Although the Z-ring has mostly been studied in chloroplasts, FtsZ has

Table 1 Plastid division components and their known properties

Machinery	Protein	Suborganellar localization	Evolutionary origin	Biochemical activity	Interacting partners	References
Stromal	FtsZ1-1 FtsZ2-1	Z-ring, inner envelope	Cyanobacteria	GTPase	MinD, MinE, ARC3	Osteryoung and Vierling (1995), Osteryoung et al. (1998)
	AtMinD1	Polar ends	Cyanobacteria	ATPase	MinE, ARC3, MCD1, CDP1	Colletti et al. (2000), Dinkins et al. (2001)
	AtminE1	Polar ends	Cyanobacteria	N/A	MinD, ARC3	Itoh et al. (2001), Maple et al. (2002)
	ARC3	Polar ends, inner envelope	Eukaryotic	N/A	MinD, MinE, PARC6	Pyke and Leech (1994), Shimada et al. (2004), Maple et al. (2007)
	ARC6	Inner envelope	Cyanobacteria	N/A	PDV2	Pyke et al. (1994), Vitha et al. (2003)
	GC1	Inner envelope	Cyanobacteria	Epimerase[a]	No interaction shown	Maple et al. (2004), Raynaud et al. (2004)
	PARC6	Inner envelope	Eukaryotic	N/A	ARC3, PDV1	Glynn et al. (2009)
	MCD1	Inner envelope	Eukaryotic	N/A	MinD	Nakanishi et al. (2009)
	AtCDP1	Inner envelope	Cyanobacteria	N/A	ARC3	Zhang et al. (2009)
Cytosolic	ARC5	Outer envelope	Eukaryotic	GTPase[a]	PDV1, PDV2	Pyke and Leech (1994), Gao et al. (2003)
	PDV1	Outer envelope	Eukaryotic	N/A	PARC6, ARC5	Miyagishima et al. (2006), Glynn et al. (2009)
	PDV2	Outer envelope	Eukaryotic	N/A	ARC6, ARC5	Miyagishima et al. (2006), Glynn et al. (2009)
Associated proteins	CRL	Outer envelope	Eukaryotic	N/A	No interaction shown	Asano et al. (2004)
	KASI	Membrane	Eukaryotic	Synthase	FtsZ1, FtsZ2, MinD, MinE	Wu and Xue (2010)
	CLMP1	Discrete foci in cytoplasm	Eukaryotic	N/A	No interaction shown	Yang et al. (2011)
	CAA33	Not known	Eukaryotic	N/A	No interaction shown	Šimková et al. (2012)
	CJD1	Inner envelope	Prokaryotic	Lipid metabolism	ARC6	Ajjawi et al. (2011)

[a] Tentative activity

been shown to play significant roles in other plastid types. For example, FtsZ is involved in amyloplast division and in the synthesis of a septum-like structure between amyloplast granules (Yun and Kawagoe 2010). In contrast to bacteria, algae and plants contain two functionally distinct FtsZ proteins, FtsZ1 and FtsZ2, which have most probably evolved through gene duplication (Osteryoung et al. 1998; Osteryoung and McAndrew 2001; Stokes and Osteryoung 2003; Miyagishima et al. 2004). In *Arabidopsis,* AtFtsZ1 and AtFtsZ2 appear promiscuous forming both homodimers and heterodimers and where polymerization can also lead to filament formation and minicircles given the appropriate stromal conditions and FtsZ levels (Erickson et al. 1996; Maple et al. 2005).

Biochemically, the plant FtsZ proteins behave in a similar fashion to bacterial FtsZ where both FtsZ1 and FtsZ2 are capable of binding and hydrolysing GTP, albeit at a lower rate compared with bacterial FtsZ (Smith et al. 2010; Olson et al. 2010). Recently, the enzymology of the plant FtsZs and how this relates to function has been under scrutiny. Early reports documented that not only does AtFtsZ1 from *Arabidopsis thaliana* have 5-times higher GTPase activity compared with AtFtsZ2 but also the two FtsZ proteins appear to regulate division through different polymerization mechanisms (El-Kafafi et al. 2005). El-Kafafi et al. (2005) showed that AtFtsZ1, but not AtFtsZ2, undergoes GTP-dependent polymerization and that AtFtsZ2 promotes AtFtsZ1 assembly in the absence of GTP. Interestingly, it has further been demonstrated that the two plant FtsZs are not interchangeable despite their conserved nature and similar biochemical activities (Schmitz et al. 2009). Indeed, AtFtsZ1 rings do not form in the absence of AtFtsZ2; however, AtFtsZ2 can form ring-like structures in the absence of AtFtsZ1. Recently, the group of Osteryoung extended this analysis and showed through a comprehensive study that both AtFtsZ1 and AtFtsZ2 bind GTP and assemble into thin protofilaments via a GTP-dependent pathway in the presence of calcium (Olson et al. 2010). However, in the

absence of calcium both FtsZ proteins show elevated GTPase activity where they coassemble into bundled protofilaments, a reaction enhanced by FtsZ1 suggesting lateral interactions between the filaments. As documented previously (Maple et al. 2005) it was conclusively shown that FtsZ1 and FtsZ2 form heteropolymers (Olson et al. 2010).

It is reasonable to assume that the GTPase activity of plant FtsZs is regulated in line with its central role in the division process. Indeed, in bacteria it has been demonstrated that FtsZ is phosphorylated and that phosphorylation leads to GTP hydrolysis impairment and reduced FtsZ polymerization ability (Thakur and Chakraborti 2006). In addition, FtsZ phosphorylation disrupts interactions with cell division proteins such as FipA (Sureka et al. 2010). We have recently shown that AtFtsZ2 in *Arabidopsis* is phosphorylated in vivo and that altered phosphorylation patterns impair Z-ring formation, similar to the situation observed in bacteria (Gargano et al. 2012). However, in contrast to bacteria inappropriate phosphorylation of AtFtsZ2 does not disrupt interactions with wild-type AtFtsZ proteins nor with ARC6 (Gargano et al. 2012).

In order for symmetrical division to occur, the precise placement of the Z-ring is essential during bacterial cell division as well as during plastid division. In bacteria, the entire membrane is competent for Z-ring formation but the coordinated action of the Min proteins position the Z-ring to the midpoint. The elegant interplay and accurate temporal and spatial relationship between the Min proteins in *E. coli* is well established. In the presence of ATP, membrane-bound MinD interacts with MinC, an inhibitor of FtsZ polymerization, preventing the formation of a Z-ring at the polar ends of the cell and subsequent asymmetrical division (Szeto et al. 2002; Hu and Lutkenhaus 2003; Zhou and Lutkenhaus 2004). MinE, a topological specificity factor, can then interact with membrane-bound MinC-MinD, activating MinD ATPase activity leading to MinD membrane dissociation, ultimately causing MinD to oscillate to the opposite side of the cell. This, in effect, results in the lowest MinC-MinD concentration at the cell midpoint, ensuring appropriate Z-ring placement (Hu and Lutkenhaus 2001; Hale et al. 2001; Meinhardt and De Boer 2001; Hu et al. 2002).

In silico and functional studies have clearly identified MinD and MinE as part of the plastid division process; however, no MinC homolog appears to be present in any plant genome analysed (Colletti et al. 2000; Maple et al. 2002). AtMinD1 in *Arabidopsis* has retained its ability to hydrolyze ATP, and AtMinD activity is activated by calcium and further stimulated by its interaction with AtMinE1 (Aldridge and Møller 2005). Interestingly AtMinD1 active site mutations do not inhibit dimerization but loss of AtMinE1 interaction, which leads to mislocalization and improper Z-ring placement followed by asymmetric plastid division. This underlines that the ATPase activity of AtMinD1 and its interaction with AtMinE1 are essential for appropriate plastid division and that the enzymology of the Min system in plants has retained, at least in part, its prokaryotic blueprint. However, for the Min system to act as a mediator of Z-ring placement a MinC-like function is required. ARC3 is a stromal plastid protein that can interact with FtsZ, AtMinD1 and AtMinE1, and based on the observation that ARC3 overexpression inhibits plastid division and that low ARC3 levels cause Z-ring misplacement it is possible that ARC3 plays a role similar to that of bacterial MinC (Maple et al. 2007).

One of the defining features of plastid division compared with bacterial cell division is the necessity for cytoplasmic influence on the division process. ARC5 (Dynamin Related Protein 5B–DRP5B) is a member of the dynamin superfamily of the eukaryotic membrane remodelling GTPases and represents a eukaryotic-specific, cytosolic component of the division machinery (Gao et al. 2003; Miyagishima et al. 2003). The recruitment of ARC5 to a discontinuous ring-like structure at the division site on the outer plastid envelope implies its involvement in constriction (Miyagishima et al. 2003). It is likely that ARC5 is capable of hydrolyzing GTP and that the enzymatic activity of ARC5 contributes to the division process. In support of this notion it has been demonstrated that binding and hydrolysis of GTP leads to dynamin disassembly and that the presence of GTP during assembly is necessary for fission competence of the polymer (Warnock et al. 1996; Pucadyil and Schmid 2008).

Giant Chloroplast 1 (GC1) is a stromal protein that localizes uniformly to the inner chloroplast envelope and where reduced levels of GC1 lead to defective plastid division characteristics (Maple et al. 2004). At the amino acid level GC1 shows 40 % similarity to prokaryotic nucleotide-sugar epimerases and ~80 % structural similarity within the active site region (Maple et al. 2004). Interestingly, GC1 does not interact with any of the known plastid division proteins suggesting that its mode of action may fall outside the main division pathway (Maple et al. 2004). Although GC1 epimerase activity has not been confirmed, it is possible that GC1 is involved in carbohydrate metabolism affecting chloroplast membrane characteristics ultimately involved in the plastid division process. Indeed, a chloroplast UDP-glucose epimerase *Arabidopsis* mutant harbours reduced monogalactosyldiacylglycerol levels, a major chloroplast membrane galactolipid, which leads to impaired chloroplast function (Li et al. 2011).

Protein complex assembly and regulation

Most of the plastid division proteins identified to date form protein complexes not only fulfilling structural obligations

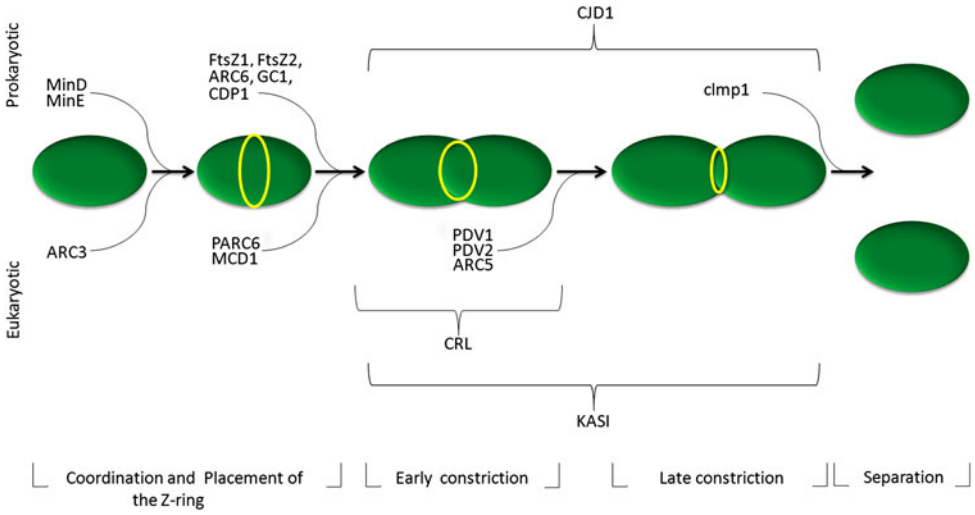

Fig. 1 Schematic diagram showing the plastid division pathway and the protein components involved in the process. The evolutionary origins of the different proteins are indicated and their temporal placement during the pathway is shown

but also regulatory roles. As plastid division is executed through the concerted action of both stromal and cytosolic protein machineries, it is prudent to describe our current understanding in terms of this spatial separation and also in terms of coordination between them.

As one might expect the stromal plastid division machinery harbours many similarities to the bacterial cell division machinery (Fig. 1). However, there are also evolutionary-driven differences. In prokaryotes a single FtsZ protein is sufficient to allow for division but where plants and algae have evolved to encode two families of FtsZ, FtsZ1 and FtsZ2 (Osteryoung et al. 1998; Stokes and Osteryoung 2003). In *E. coli* FtsZ clearly plays a scaffolding role recruiting cell division proteins to the site of constriction (Margolin 2005). Plant FtsZs have a similar role but also have the added complexity of having two members that need to interact in the correct constellations. It has conclusively been shown that FtsZ1 and FtsZ2 can interact forming both homo- and heterodimers (Maple et al. 2005) and recent studies have further demonstrated that FtsZ1 and FtsZ2 form bundled protofilaments influenced by calcium and affecting GTPase activity (Olson et al. 2010). Elegant biochemical and biophysical studies by the group of Holzenburg established that FtsZ from *Arabidopsis* assemble into type-1 and type-II filaments in the presence of GTP (Smith et al. 2010), that both FtsZ1 and FtsZ2 are homodimers prior to assembly and that during early stages of FtsZ type-II filament assembly FtsZs are found predominantly as tetrameric intermediates (Smith et al. 2011). Although it is still unclear whether the FtsZ heteropolymers consist of homodimeric units or whether FtsZ1-FtsZ2 heterodimers are also part of the filaments, the results combined demonstrate that FtsZs in higher plant chloroplasts follow a strict assembly pathway influenced by cations and its enzymatic activity.

As in bacteria the plant FtsZs can interact with other protein components involved in division. ARC6 encodes a J-domain plastid division protein, a descendant of the cyanobacterial cell division protein Ftn2, which has the ability to interact with FtsZ2 (Vitha et al. 2003; Maple et al. 2005; McAndrew et al. 2008). This interaction has been shown to stabilize the Z-ring suggesting an evolutionary conservation of this central mechanism from cyanobacteria to higher plants. Interestingly, FtsZ2 is associated with both the chloroplast envelope and thylakoid membranes (El-Kafafi et al. 2005, 2008) and merged with the fact that ARC6 interacts with the Chloroplast J-like Domain 1 protein, involved in chloroplasts lipid metabolism (Ajjawi et al. 2011), it is tempting to speculate that there is a link between plastid division and membrane biogenesis/maintenance through the formation of higher order protein complexes. Further support for this has come from a study of *Arabidopsis* mutants deficient in polyunsaturated fatty acids in chloroplast membrane lipids where chloroplast division is also compromised (Fan and Xu 2011). Combined, it is possible that an inadequate supply or altered composition of lipids limits membrane proliferation which is needed during the plastid division process.

The stabilization of the Z-ring, mediated by ARC6, dictates the need for a destabilization mechanism. Indeed, PARC6, a paralogue of ARC6, has been shown to localize to the inner chloroplast envelope where it destabilizes the Z-ring but not through a direct interaction with FtsZ (Glynn et al. 2009). PARC6 does, however, interact with ARC3, which also has the ability to interact with FtsZ1 (Maple et al. 2007; Glynn et al. 2009), suggesting that Z-ring destabilization may be mediated through ARC3. ARC3 has two main domains, a non-catalytic N-terminal FtsZ-like domain and a C-terminal Membrane Occupation and Recognition Nexus domain (MORN). This FtsZ-like domain has most probably evolved to mediate interaction with FtsZ1 whilst the MORN domain may have a role in mediating the destabilization mechanism.

To add to the complexity ARC6 can also interact with Cdc10-dependent transcript 1, a dual nuclear and plastidic localized protein part of a pre-replication complex (Raynaud et al. 2005). Interestingly, Cdc10-dependent transcript 1 down-regulation affects not only nuclear DNA replication but also plastid division suggesting a link between nuclear and plastidic events. However, the precise mechanics are unknown, but it represents a starting point for further studies into possible nuclear-plastid communication processes that influence and possibly regulate plastid division.

Clearly Z-ring formation involves a combination of controlled enzymatic activities and the formation of elaborate protein complexes. Equally important is the correct placement of the Z-ring. In bacteria the Min proteins fulfil this role (de Boer et al. 1989) as is also the case in algae and higher plant plastids (Colletti et al. 2000; Itoh et al. 2001; Maple et al. 2002; Adams et al. 2008). As described earlier, the AtMinD1 ATPase activity is stimulated by AtMinE1 in *Arabidopsis* (Aldridge and Møller 2005), and the AtMinD1/AtMinE1 interaction is mediated through a C-terminal amphipathic helix on AtMinE1 (Maple et al. 2005; Maple and Møller 2007). The combined action of the AtMinD1/AtMinE1 complex is essential for correct Z-ring placement (Maple et al. 2002, 2007). For the Min system to operate appropriately, however, it requires a component which affects FtsZ polymerization, a function performed by MinC in bacteria (de Boer et al. 1988, 1989; Hu and Lutkenhaus 1999). As higher plants do not harbour a classical MinC it is thought that ARC3 may have recruited this role (Maple et al. 2007). Apart from its interaction with FtsZ1, ARC3 also interacts with AtMinD1 and AtMinE1 (Maple et al. 2007), and ARC3 down-regulation shows misplaced Z-rings similar to that observed in *Arabidopsis* plastids harbouring inappropriate levels of AtMinD1 and AtMinE1 (Maple et al. 2002; Fujiwara et al. 2004). Perhaps ARC3 regulates the relationship between the Min system and proteins involved in Z-ring stabilization/destabilization.

Multiple Chloroplast Division 1 (MCD1) represents another plant-specific protein localised to the inner envelope with a coiled-coil domain present in the stroma (Nakanishi et al. 2009). MCD1 can interact with AtMinD1 leading to division site recruitment and subsequent regulation of Z-ring placement. Similar to the postulated ARC3 mode of action MCD1 represents another possible mechanism mediating Z-ring placement, which is different from that observed in bacteria.

It is evident that multiple mechanisms have evolved in plants that are either directly or indirectly involved in Z-ring placement (Fig. 1). Apart from ARC3 and MCD1 the Chloroplast Division site Positioning 1 (AtCDP1) protein in *Arabidopsis* has also been shown to be associated with Z-ring placement (Zhang et al. 2009). In line with previous findings, AtCDP1 interacts with ARC3 suggesting the presence of a Min/ARC3/AtCDP1 protein complex mediating correct Z-ring placement.

Plastid division has also evolved a cytosolic division machinery which has presumably enhanced the ability of the division process to be integrated into a eukaryotic context. The first evidence for a cytosolic division machinery came from the observation that one of the electron-dense plastid dividing (PD) rings was associated with the cytosolic surface of the outer chloroplast envelope at the central constriction site (Hashimoto 1986). Relatively limited information exists on PD ring biology; however, the reported observations no doubt spurred interest in identifying cytosolic plastid division players and protein complexes.

ARC5 represents the first *bone fide* cytosolic plastid division component identified where ARC5 deficiency results in plastid division arrest during late constriction (Gao et al. 2003). The precise and temporal localization dynamics of ARC5 from the cytosol to the outer envelope constriction site raised questions regarding recruitment mechanisms. From analysis of *Arabidopsis* mutants displaying *arc5*-like phenotypes, PLASTID DIVISION 1 (PDV1) and PDV2 were identified (Miyagishima et al. 2006). PDV1 and PDV2 are integral outer envelope membrane proteins where PDV1 forms a discontinuous ring structure at the division site similar to ARC5 (Fig. 1). Interestingly, PDV1 rings are able to form in the *arc5* mutant background whilst ARC5 is unable to assemble into a ring in the *pdv1/pdv2* background. This leads to a model suggesting that during constriction ARC5 is recruited from the cytosol to the division site by PDV1 and PDV2 to form a ring structure during late stage division. Further work demonstrated that PDV1 constriction site localization is dependent on PARC6 whilst PDV2 localization is dependent on ARC6 (Miyagishima et al. 2006; Glynn et al. 2009). ARC6 can indeed interact with PDV2 within the intermembrane space where loss of interaction results in PDV2 mislocalization followed by loss of ARC5 recruitment (Miyagishima et al. 2006). The fact that ARC6 promotes stromal Z-ring assembly demonstrates a direct communication and coordination between the cytosolic and stromal division machineries. PDV1 does not interact with ARC6 but is recruited to the constriction site by PARC6 (Glynn et al. 2009). As PARC6 interacts with stromal ARC3 and appears to inhibit Z-ring assembly, it is evident that ARC6 and PARC6 have antagonistic effects on constriction through overlapping but yet distinct functions.

The cytosolic plastid division machinery, mediated through the PDV proteins, is also involved in determining chloroplast division rates (Okazaki et al. 2009). It has been demonstrated that increased levels of PDVs in both *Arabidopsis* and moss increases the number of chloroplast with a

concomitant decrease in chloroplast size. In agreement, PDV protein levels decrease during leaf development when chloroplast division rates decline. Perhaps, not totally unsurprisingly, exogenous cytokinins increased chloroplast division rates as also observed in plants overexpressing the cytokinin-responsive transcription factor CYTOKININ RESPONSE FACTOR 2 (Okazaki et al. 2009). These results demonstrate a molecular regulation of chloroplast size and number in relation to cell differentiation.

Integration of plastid division into a multicellular context

Plastid division is often viewed as a semi-autonomous process. However, the replication of plastids fulfils an integrated function during development and differentiation in higher plants. Indeed, plastid division must keep abreast with cell division to ensure a full organelle quota in the resulting daughter cells. With respect to this plastid division occurs at specific stages of the cell cycle in many algae where the division and segregation of a single chloroplast is essential during cell division (Takahara et al. 2000; Adams et al. 2008; Fujiwara et al. 2009). In higher plants, however, plastids appear to divide in a nonsynchronous manner and are most probably not regulated by the cell cycle. How is plastid division then regulated? It is clear that control mechanisms are in place as both the chloroplasts size and number change during cell differentiation. For instance, there is a relationship between the cell cycle and proplastid division in meristematic tissue (Seguí-Simarro and Staehelin 2009) where 10–20 proplastids are maintained at any one time. As these meristematic cells then differentiate and develop into leaf cells, proplastids differentiate into chloroplasts followed by increased division leading to a full complement of chloroplast per leaf cell often exceeding one hundred chloroplasts (Pyke et al. 1999). Conversely, as leaf development proceeds chloroplast division rates decrease. The exact regulatory circuits involved are unknown although it is evident that the PDV proteins are involved as is cytokinin (Okazaki et al. 2009).

CRUMPLED LEAF (CRL) seems to represent a link between plastid and cell division in higher plants as a *crl* *Arabidopsis* mutant shows morphological abnormalities due to aberrant cell division and differentiation (Asano et al. 2004). Interestingly, this mutant also harbours a reduced number of enlarged plastids suggesting that CRL is involved in plastid division and in cell differentiation and regulation of the cell division plane in plants.

The identification of clumped chloroplasts 1 (clmp1) suggests a relationship between the cell cycle and plastid segregation where a loss-of-function mutant in *Arabidopsis* leads to chloroplasts clustering in the cytoplasm (Yang et al. 2011). This effect is only observed at specific developmental stages and indeed immature petioles harbour cells completely lacking chloroplasts due to inappropriate segregation. The data suggest that there are regulatory processes in place that ensures plastid distribution and partitioning during cell division.

The plastid stroma not only contains elaborate internal thylakoid membranes but is also enclosed by a double-membraned envelope. During plastid division, appropriate membrane biosynthesis is presumably required to accommodate for the expansion of the plastid membrane surface area and for the biosynthesis of new thylakoid membranes in the two daughter chloroplasts. β-Ketoacyl-[acyl carrier protein] synthase I (KASI) catalyses the elongation of fatty acid synthesis and a KASI *Arabidopsis* mutant shows pleiotropic plant growth effects and disrupted chloroplast division (Wu and Xue 2010). Indeed, KASI-induced alterations in the polar lipid composition not only suppress the expression of *FtsZ* and *Min* genes but also lead to disordered Z-ring placement and FtsZ polymerization inhibition. Combined with data indicating that an inadequate supply or altered composition of lipids limits membrane proliferation during plastid division (Ajjawi et al. 2011; Fan and Xu 2011), it appears that an exciting new angle to regulatory aspects of plastid division has been discovered.

As plants are highly adaptable to exogenous cues it has been suggested that environmental stimuli may have an effect on chloroplasts division rates (Lopez-Juez and Pyke 2005). No conclusive studies have linked the impact of changing environmental conditions on plastid division; however, it is tempting to speculate that this is, however, the case. Certainly, one would assume that light conditions have an effect on chloroplast numbers not only in terms of reaching full photosynthetic competency but also to minimize photo-oxidative damage during excess light (Jeong et al. 2002).

Concluding remarks and future directions

Plastid division is clearly a complex process involving the coordinated action of evolutionary conserved and host-derived components across a double-membraned structure (Fig. 1). Numerous *bone fide* plastid division proteins have been isolated and characterised (Table 1) and our knowledge of precise mechanisms and indeed the spatial and temporal relationship of the components is being unravelled. Undeniably, the more recent findings that proteins associated with fundamental plant processes, such as the cell cycle and fatty acid/lipid metabolism, also impact plastid division not only furthers our understanding of the process but also underlines the cellular integration of plastid division. Despite this many questions remain unanswered.

As all plastid division proteins identified to date are nuclear encoded it would be reasonable to assume that retrograde signalling is part of the plastid division control circuitry. Indeed, the Constitutive Activator of AAA-ATPase (CAA33) is not only involved in plastid division but also mediates plastid signalling to the nucleus to induce stress acclimation (Šimková et al. 2012). Despite this genome-wide gene expression profiling in response to altered plastid division characteristics in *Arabidopsis* revealed a remarkably low number of genes affected by altered division status (Maple et al. 2011). This indicates that regulatory mechanisms may be at the protein level, but it also exposes the fact that plastid division control is more complex than first anticipated.

How plastid division is fully integrated into the developmental programme of plants and how the process adapts to plant plasticity in response to environmental changes still requires further investigation. Studies have shown the influence of at least one plant hormone (Okazaki et al. 2009), which provides an excellent starting point.

A wishful scenario within the field would be the ability to construct a plastid division reconstitution system where plastid division could be followed temporally and where parameters could be analysed. We are not there yet. However, by combining our current knowledge with emerging new approaches and utilizing the battery of molecular reagents available plastid division and its regulation is clearly under scrutiny.

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