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Recent Advances in Chloroplast and Mitochondrial Division

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ABSTRACT

The division of endosymbiotic organelles (mitochondria and chloroplasts, which are derived from the ancient engulfment of free-living bacteria) are complex processes requiring proteins derived from the host and symbiont. The last 12 months have seen great leaps forward in our understanding of these processes including a more detailed understanding of the components required for the recruitment of dynamin-like proteins, the elucidation of the division components applying the constrictive force required for organelle division, the discovery of an Fzo-like protein in chloroplasts and new evidence questioning the evolutionary origins of the dynamins. Here we discuss recent findings in light of our current understanding of the chloroplast and mitochondrial division processes.

Keywords: BDLP, Dnm1, Fis1, FtsZ, Mdv1, mitochondrial fusion

Abbreviations: BDLP, bacterial dynamin-like protein; **cp**, chloroplast targeted; **DLP**, dynamin-like protein; **IM**, inner membrane; **IMS**, inter membrane space; **MD**, mitochondrial-dividing; **mt**, mitochondrially targeted; **OM**, outer membrane; **PD**, plastid-dividing; **PDF**, chloroplast division machinery

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INTRODUCTION

Mitochondria and chloroplasts arose from the endosymbiotic uptake of an α-proteobacterium and cyanobacterium, respectively. Though of independent origins, these organelles have evolved similar modes of replication. Propagation of mitochondria and chloroplasts results from the division of pre-existing organelles. In the original symbioses, it is believed that these organelles maintained their own metabolism, division and genomes, but evolution has since seen the condensation of these genomes as many of the genes have been lost or transferred to the host nucleus (Timmis *et al*. 2004). Most proteins essential for organelle function, including those for division, are now translated by the host and delivered back to the organelle using a complex targeting and import system (Dyall *et al*. 2004; Embley and Martin 2006).

Today, mitochondria and chloroplasts are double-membrane bounded organelles with an outer membrane (OM), inter membrane space (IMS), an inner membrane (IM), and an internal compartment called the matrix (mitochondria) or stroma (chloroplasts). We note, though, that many (mostly golden-brown) chloroplasts and plastids are bounded by more than two membranes due to secondary endosymbiosis (for review, see Palmer 2003). While they were acquired roughly one billion years apart (Dyall *et al*. 2004), chloroplasts and the mitochondria of some eukaryotes reveal their prokaryotic origins in the proteins used for their division. The most widespread division protein of bacterial origin is FtsZ, a structural homolog of tubulin (Löwe and Amos 1998). FtsZ contains an N-terminus, core region, variable spacer and a C-terminal peptide. The N-terminus and variable spacer regions are highly inconsistent in size and have unknown functions, while the core domain (containing a GTPase motif and showing the highest homology to tubulin) is required for GTP hydrolysis and polymerisation (Margolin 2005). In contrast to most bacteria, chloroplasts and possibly mitochondria contain two families of organelle-targeted FtsZ. Both have a similar structure to bacterial FtsZ except that one of the families, FtsZ1 in plants, lacks the C-terminal core domain – a site of protein-protein interactions (Osteryoung and McAndrew 2001; Kiefel *et al*. 2004; Miyagishima *et al*. 2004). Purified *Escherichia coli* FtsZ is able to form polymers *in vitro* which display tubulin-like structures such as protofilaments, bundles and mini-rings (reviewed in Margolin 2005). FtsZ subunits or small protofilaments exhibit rapid helical movement within *E. coli* (Thanedar and Margolin 2004), polymerising to form what is commonly termed the FtsZ- or Z-ring at the equator of the cell (Bi and Lutkenhaus 1991). Correct placement of the FtsZ-ring is determined by nucleoid occlusion and the action of the Min family of proteins (Margolin 2005; Vicente *et al*. 2006) homologs of which, with the exception of MinC, are involved in chloroplast division (Osteryoung and Nunnari 2003).

Immunofluorescence, immunoelectron and most recently cryo-electron microscopy of vitreous sections (Zuber *et al*. 2006) have shown the bacterial FtsZ-ring localised to the

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cytoplasm in close association with the cytoplasmic membrane, where (in *E. coli*) it is tethered by ZipA and FtsA via its C-terminus (Hale and de Boer 1997; Pichoff and Lutkenhaus 2005). It remains to be determined whether the FtsZ-ring provides the contractile force required for division, or whether it acts as a scaffold to which other division proteins bind (of which around a dozen have been described; Vicente *et al*. 2006). The study of bacterial fission has provided many insights into the division mechanisms that chloroplasts and mitochondria employ to maintain organelle number within a cell (Kiefel *et al*. 2006; Machida *et al*. 2006; Maple and Möller 2007).

CHLOROPLAST AND MITOCHONDRIAL DIVISION – CONCENTRIC CIRCLES

Green chloroplasts contain two distinct families of FtsZ: FtsZ1 and FtsZ2 (Osteryoung *et al*. 1998; Stokes and Osteryoung 2003). Both FtsZ1 and FtsZ2 are required for successful chloroplast division since anti-sense disruption of either *ftsZ* gene inhibits organelle division (Osteryoung *et al*. 1998).

Mitochondrial *ftsZ* genes are found in diverse species of protist (Beech *et al*. 2000; Takahara *et al*. 2000; Kiefel *et al*. 2004; Miyagishima *et al*. 2004) but they are absent from the genomes of animals, plants and fungi. In many protists, a single copy of mitochondrially targeted (mt) FtsZ has been identified, however, in other species, two have been noted (Gilson *et al*. 2003; Miyagishima *et al*. 2004; Kiefel *et al*. 2006). Similar to bacterial FtsZ, both chloroplast and mitochondrial FtsZs localise early to the site of division where they form bands or puncta (Beech *et al*. 2000; McAndrew *et al*. 2001; Nishida *et al*. 2003). An exception being in the slime mould, *Dictyostelium discoideum*, where one mt-FtsZ, FszB, localises to a sub-mitochondrial body at the organelle's pole, suggesting a novel role for FszB within organelle division (Gilson *et al*. 2003).

An excellent model for the study of chloroplast and mitochondrial division is the red alga, *Cyanidioschyzon merolae*. This small readily synchronized unicell contains a single mitochondrion and chloroplast. It was in *Cyanidium caldarium* RK-1, a close relative of *C. merolae*, that electron-dense bands were first discovered at the division furrow of chloroplasts (Mita *et al*. 1986). These bands were termed plastid-dividing (PD) rings and have since been found in a variety of organisms (Maple and Möller 2007). Plastid-dividing rings consist of an inner PD ring on the stromal face of the IM and an outer PD ring on the cytosolic face of the OM (**Fig. 1**). A third PD ring has since been localised to the IMS in the chloroplast of *C. merolae* (Miyagishima *et al*. 1998). The PD rings are distinct from the rings formed by either FtsZ (Miyagishima *et al*. 2001a) or dynamin-like proteins (DLPs) (Miyagishima *et al*. 2003) and their composition is unknown. During constriction of the chloroplast, PD ring formation occurs after FtsZ ring assembly but precedes the recruitment of DLPs. Structures similar to PD rings, called mitochondrial-dividing (MD) rings, were observed at the site of mitochondrial division in *C. merolae* (Kuroiwa *et al*. 1993) and the higher plant *Pelargonium zonale* (Kuroiwa *et al*. 2006). Electron-dense

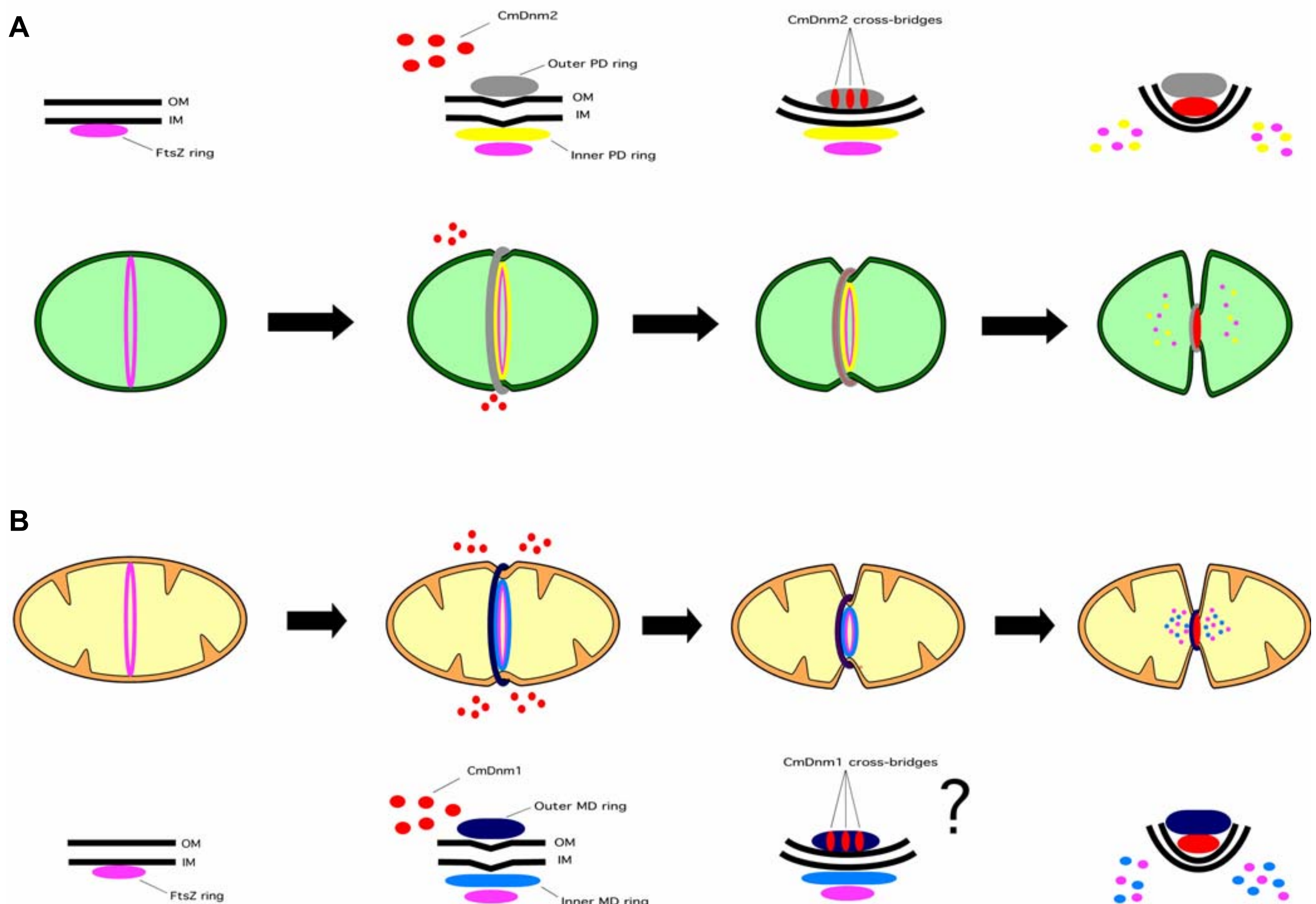

Fig. 1 Comparison of chloroplast and mitochondrial division in *C. merolae*. Chloroplast division of *C. merolae* (**A**) shows early formation of the FtsZ ring, followed by assembly of the inner and outer PD rings respectively (a third PD ring located within the IMS of *C. merolae* has not been shown). CmDnm2 is recruited from the cytosol to provide cross-bridging between outer PD ring filaments to impart the constrictive force required for organelle division. Late in division, FtsZ and the inner PD ring are distributed to the daughter organelles before final membrane severance by CmDnm2. (**B**) The formation of the FtsZ-ring early in mitochondrial division is followed by the sequential localisation of the inner and outer MD rings. Note that MD rings have only been observed in a few organisms to date (Kuroiwa *et al*. 2006). CmDnm1 constricts the OM (possibly by acting as a cross-bridge between outer MD ring filaments) late in division to severe the daughter organelles. Components of IM division are evenly distributed between organelles before final membrane scission. Abbreviations: IM, inner membrane; IMS, inter membrane space; OM, outer membrane.

structures have also been observed in the dividing mitochondria of yeast (Ingerman *et al*. 2005) and human cells (Yoon *et al*. 2003) though MD rings, if present, remain difficult to detect with current techniques.

Dynamins and DLPs are GTPases found in a wide range of organisms where they are involved in various membrane remodelling processes throughout the cell (Praefcke and McMahon 2004; Kuravi *et al*. 2006). It has now become apparent that DLPs also act in the division of both mitochondria and chloroplasts: they are recruited from the cytosol to organelle division sites after the formation of the Z-ring, inner- and outer-PD rings (or MD rings, if present), and after the initial constriction (for example in *C. merolae*; **Fig. 1**). The chloroplast-targeted (cp) DLPs, ARC5 (in *Arabidopsis thaliana*) and CmDnm2 (in *C. merolae*), accumulate as patches on the external surface of the chloroplast before forming an equatorial band late in the division process to presumably pinch off the two daughter organelles (Gao *et al*. 2003; Miyagishima *et al*. 2003). This process is mechanistically similar to the action of Dnm1 and CmDnm1, DLPs involved in the mitochondrial division of yeast and *C. merolae*, respectively (Legesse-Miller *et al*. 2003; Nishida *et al*. 2003). Interestingly, while the bands formed by mt-DLPs at the site of division display solid intensity, cp-DLPs show bands that are speckled, suggesting that they are discontinuous or not of uniform composition (Gao *et al*. 2003; Miyagishima *et al*. 2003).

Mutations in the DLPs required for chloroplast and mitochondrial division result in differing morphologies. Mutations in cp-DLPs lead to fewer and larger chloroplasts that display a dumbbell morphology, indicative of a failure late in the division process (Gao *et al*. 2003). Alternatively, when *dnm1* is mutated in yeast, mitochondrial division is halted (Otsuga *et al*. 1998), with the mitochondria collapsing to one side of the cell forming a network morphology through unopposed fusion reactions (Bleazard *et al*. 1999; Sesaki and Jensen 1999). Yeast mitochondria deficient for division still retain tubular mitochondria (even if networked) due to proteins involved in the tubulation pathway (Okamoto and Shaw 2005). This pathway is absent in chloroplasts, which rely on MscS-like proteins, among others, to control organelle size and shape (Haswell and Meyerowitz 2006).

THE FORCE IS WITH… WHO?

Among the myriad of organelle division proteins, it has, until recently, been unclear which of the division components actually applied the force required for organelle constriction. Studies of DLPs and dynamins *in vitro* indicate that they are capable of self-assembly to form higher order structures such as filaments, rings and spirals (Warnock *et al.* 1996; Sever *et al.* 1999; Marks *et al.* 2001; Ingerman *et al.* 2005). *In vitro* the self-assembly of dynamin can constrict spherical lipid vesicles to form dynamin-lipid tubules that, upon addition of GTP, constrict and fragment (Sweitzer and Hinshaw 1998; Takei *et al.* 1998). Despite the apparent mechanochemical role of dynamin within the cell, one cannot discount the possibility that other proteins may be involved in applying (or contributing to) the constrictive force required for membrane severance. Studies have suggested that dynamin may act as a classic signalling GTPase which recruits downstream effectors that are responsible for membrane division (Sever *et al.* 1999, 2000; Newmyer *et al.* 2003), while the yeast mitochondrial DLP (Dnm1) can only bring about organelle division in the presence of Fis1 and Mdv1 (discussed below). Though it is generally accepted that chloroplasts and mitochondria require DLPs for final organelle severance, Yoshida *et al.* (2006) have proposed a novel mechanism for DLP early in chloroplast constriction, having isolated the chloroplast division machinery (PDF machinery consisting of PD rings, DLP, and FtsZ rings) from dividing chloroplasts of synchronized *C. merolae* cells (Yoshida *et al*. 2006). Upon removal of the OM, isolated PDF machineries formed super-twisted rings, circular rings, and spirals. FtsZ-released and intact PDF machineries continued to show spiral structures, whereas DLP-released PDF machineries became straight. Spiral PDF machineries were able to be stretched to four times their original length, yet were able to return to their original size upon release – even after repeated stretches. In contrast, no such elasticity was seen in DLP-released PDF machinery, and thus DLP was considered to provide the constrictive force required for chloroplast division (Yoshida *et al*. 2006). Furthermore, immunoelectron microscopy on isolated PDF machineries from dividing chloroplasts showed that DLP was recruited to the site of division, where it appeared to act as a cross-bridge between outer PD ring filaments (**Fig. 1**) – probably aiding in the sliding of the outer PD ring filaments – and eventually formed a band for final membrane fission (Yoshida *et al*. 2006). Due to the mechanistic similarities between chloroplast and mitochondrial targeted DLPs, it is possible that DLPs play a similar role in mitochondrial division, even though MD rings remain elusive in most organisms.

Given that the outer PD ring appears to require a cross-bridging protein (Yoshida *et al*. 2006), it is feasible that the inner PD ring (though kinetically and compositionally different) will require a similar molecule. Recent findings that the role of FtsZ may be more diverse than previously thought, acting as a possible cytoskeletal component in *Nostoc*/*Anabaena* sp. (Klint *et al*. 2007), make it tempting to speculate that FtsZ may fulfil this function. Treatment with Nonidet P-40 extracts both FtsZ and the inner PD ring (Miyagishima *et al*. 2001a), while immunoelectron microscopy of *C. merolae* (Miyagishima *et al*. 2001b; Yoshida *et al*. 2006) showed FtsZ in close association with the inner PD ring. Due to the differing dynamics between the inner and outer PD rings (Miyagishima *et al*. 2001b), it is possible that FtsZ provides a small amount of constriction, creating the division furrow, thereby recruiting cp-DLP which then provides the majority of the constrictive force required for organelle division. The lack of elasticity observed upon release of DLP from the PDF machinery (Yoshida *et al*. 2006) may be attributable to the presence of the outer PD ring which masks the contractile force applied by FtsZ. Alternatively, the FtsZ-ring may be the recruitment site of an as yet unknown protein that acts as a cross-bridge, similar to the way in which the FtsZ-ring acts as the recruitment site of bacterial division proteins.

GATHERING THE NOOSE

The discovery that DLP provides the constrictive force required for chloroplast division underlines the importance of organelles' ability to recruit DLPs from the cytosol. A number of publications in 2006 characterised proteins required to recruit DLPs to the site of organelle division. The integral membrane protein Fis1 in yeast is distributed uniformly over the mitochondrial OM, where it is anchored via its C-terminus (Mozdy *et al*. 2000). The N-terminus interacts with Dnm1 and Mdv1 via a tetratricopeptide repeat domain (**Fig. 2**), a well known protein-protein interaction motif (Dohm *et al*. 2004). Homologs of Fis1 have been found in a variety of organisms, most recently in the genomes of *Arabidopsis* (BIGYIN; Scott *et al*. 2006), *Dictyostelium* and *C. merolae* (Kiefel 2006). The reliance on Fis1 to anchor Dnm1 to the outer mitochondrial membrane is demonstrated by the organelle morphologies of *fis1*Δ and *bigyin* mutant strains (in yeast and *Arabidopsis* cells, respectively) which show a mitochondrial morphology similar to that observed in yeast *dnm1*Δ cells (Mozdy *et al*. 2000) and *Arabidopsis DRP3A* (Arimura *et al*. 2004) *DRP3B* mutants (Arimura and Tsutsumi 2002).

Yeast mitochondrial division requires not only Fis1 and Dnm1 but involves two other proteins, Mdv1 and Caf4, which are thought to act as linker molecules between Fis1 and Dnm1 (Tieu and Nunnari 2000; Fekkes *et al*. 2000; Cerveny *et al*. 2001; Griffin *et al*. 2005). The domain structures of Mdv1 and Caf4 both consist of an N-terminal extension

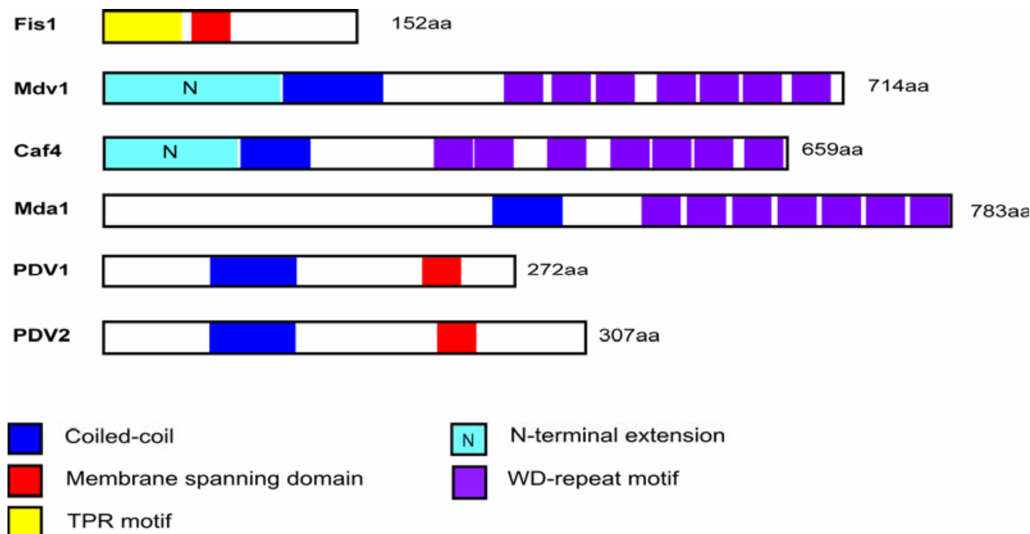

Fig. 2 Structural domains of proteins involved in the recruitment of dynamin-like proteins. While differing in their primary sequence, the proteins required to recruit DLPs to the site of organelle division show many domain similarities. The most prevalent being a coiled-coil domain present in all proteins except Fis1.

and coiled-coil regions, followed by seven WD40 repeats that are predicted to form a β-propeller at the C-terminus (Okamoto and Shaw 2005) (**Fig. 2**); however, despite their similar structures, recent studies suggest that Mdv1 and Caf4 have different cellular functions. Mdv1/Fis1 complexes are distributed uniformly over mitochondria forming punctate structures only when co-localising with Dnm1-containing fission complexes (Tieu and Nunnari 2000; Cerveny *et al*. 2001; Karren *et al*. 2005). Bhar *et al*. (2006) propose that the division complex begins by the recruitment of Dnm1 dimers to Mdv1/Fis1 complexes. The Dnm1 dimers then further assemble into multimeric complexes that drive the reorganization of Mdv1 from its uniform distribution into the punctate fission complexes, facilitating mitochondrial division (Bhar *et al*. 2006). While Caf4 shares many properties with Mdv1, both in structure and localisation, *caf4*Δ cells show a wild-type mitochondrial morphology suggesting that Caf4 acts only indirectly on mitochondrial division (Griffin *et al*. 2005). The role of Caf4 may be explained by the recent discovery of two morphologically distinct subsets of mitochondrion-associated Dnm1 assemblies. A small fraction is found in spiral-like structures at tubule constrictions (presumably associating with Mdv1 and acting in division), while the majority of Dnm1 is found in clusters that exhibit a polarized orientation facing the cell cortex (Schauss *et al*. 2006). The polarity of these clusters is dependent on Fis1 and Caf4, being abolished in either *caf4*Δ and *fis1*Δ cells but not *mdv1*Δ cells (Schauss *et al*. 2006). If Caf4 is involved in maintaining a cortical mitochondrial network, it would explain the collapsed network morphologies observed in *dnm1*Δ, *fis1*Δ, *mdv1*Δ *caf4*Δ and *mdv1*Δ *dnm1*Δ cells (Griffin *et al*. 2005; Schauss *et al*. 2006).

Lacking obvious homologs in other organisms, Mdv1 and Caf4 were thought to be unique to yeast. However, their role now appears to be served, at least in one other organism (*C. merolae*), by a structurally similar protein: Mda1 (Nishida *et al*. 2007). Mda1 has a centrally located putative coiled-coil region and seven WD40 repeat units at the C-terminal forming a β-propeller (**Fig. 2**) – similar to the architecture of Mdv1 and Caf4 (Nishida *et al*. 2007). Immunofluorescence studies on synchronized *C. merolae* cells revealed Mda1 localising to mitochondria forming a medial band as division progressed (S/G2 phase). Late in the division process (M phase), Mda1 is phosphorylated and the *C. merolae* mitochondrial DLP (CmDnm1) is recruited from the cytosol to co-localise with Mda1 (Nishida *et al*. 2007). Studies of Mdv1 and Caf4 are yet to reveal if these proteins require activation, for example, either by phosphorylation or dimeric versus multimeric Dnm1 binding, to bring about mitochondrial division.

Chloroplasts, like mitochondria, require DLPs late in division, and only recently have we begun to understand how these proteins are recruited to the organelle. PDV1 and PDV2 are the first plastid division proteins identified that are functionally involved in the recruitment of cp-DLPs (Miyagishima *et al*. 2006). PDV1 and (most likely) PDV2 are OM proteins with their N-termini and coiled-coil domains exposed to the cytosol (**Fig. 2**). The C-termini of these proteins are located in the IMS, where a conserved glycine residue ensures correct localisation to the division site, possibly through interaction with an as yet unknown protein (Miyagishima *et al*. 2006). This hypothetical protein may determine the localisation of the OM division apparatus, linking inner and outer membrane division. PDV1 and PDV2 have a functionally redundant role in the recruitment of the *Arabidopsis* cp-DLP, ARC5, though both are necessary for successful chloroplast division with single or double mutants resulting in dumbbell shaped chloroplasts (Miyagishima *et al*. 2006). Similar to ARC5-GFP, GFP-PDV1 localises to the site of plastid division after the formation of the FtsZ-ring, forming a discontinuous ring structure that increases in fluorescence intensity as division progresses (Miyagishima *et al*. 2006).

Mdv1, Caf4, Mda1, PDV1 and PDV2 all vary in size and primary sequence, but the one common structural feature that they possess is a centrally located putative coiled-coil domain (**Fig. 2**). This coiled-coil domain may have a similar function in chloroplast and mitochondrial division (Miyagishima *et al*. 2006), allowing self oligomerization or perhaps the interaction of these DLP recruitment molecules with another component of organelle division, possibly the outer MD or PD rings. Future experiments may well determine the binding partners of these proteins and thus refine our understanding of organelle division.

FUSION: THE FLIP SIDE OF DIVISION

In contrast to chloroplasts, the morphology of mitochondria is highly dynamic with balanced fission (division) and fusion reactions (**Fig. 3**) responsible for maintaining organelle number within a cell (Shaw and Nunnari 2002; Chan 2006). It is thought that mitochondrial fusion allows inter-mitochondrial cooperation by facilitating the exchange of both membrane and matrix components, helping to restore local depletions and maintaining mitochondrial function (Nakada *et al*. 2001). The benefits of fusion are exemplified by the results of Spees *et al*. (2006) who showed that aerobic respiration could be restored to cells by the transfer of mitochondria, or at least components of mitochondria. Like division, mitochondrial fusion relies on conserved GTPases and their binding partners to regulate mitochondrial number and morphology within a cell.

Two GTPases required for yeast mitochondrial fusion are Fzo1 and Mgm1. Mutations in the human orthologs of these genes, *mfn2* (one of two *fzo1* homologues) and *opa1*

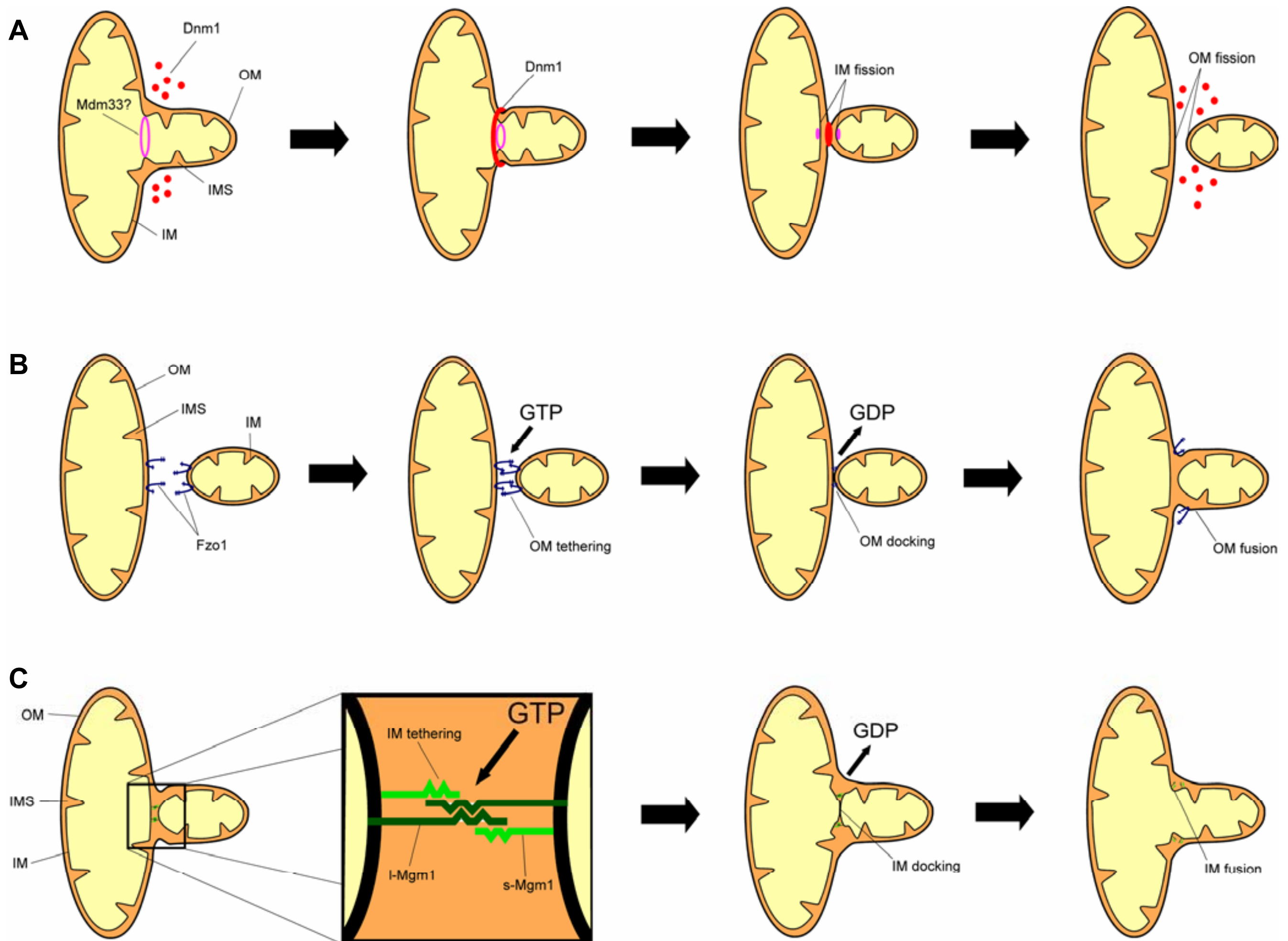

Fig. 3 Dynamics of yeast mitochondrial fission and fusion. Mitochondrial fission in yeast (**A**) requires Mdm33 for IM division. The mechanism(s) by which Mdm33 enables IM division are currently unclear. The OM division occurs via Dnm1 (a DLP) in association with Fis1 and Mdv1, forming a band late in division to bring about organelle separation. Mitochondrial fusion relies on two large GTPases – Fzo1 (Mfn1 & Mfn2) and Mgm1 (OPA1), to divide the outer (**B**) and inner (**C**) membranes respectively. Fzo1 and two isoforms of Mgm1, a longer membrane bound form (l-Mgm1) and a shorter more soluble version (s-Mgm1), fuse the membranes by first tethering opposing outer or inner membranes together via homo/heterozygous interactions. Once tethered, membranes are brought into contact (docking) via an unknown GTP dependent reaction allowing membrane fusion. Abbreviations: IM, inner membrane; IMS, inter membrane space; OM, outer membrane.

(*mgm1*), cause two distinct neurodegenerative diseases, Charcot-Marie-Tooth neuropathy type 2A (CMT2A) (Züchner *et al*. 2004) and dominant optic atrophy (Alexander *et al*. 2000; Delettre *et al*. 2000) respectively. Mutations in *mfn2* not only lead to CMT2A (Züchner *et al*. 2004) but can cause dominant optic atrophy, revealing a functional overlap with *opa1* (Züchner *et al*. 2006). Of interest is the recent report that complementation between animal Fzos, Mfn1 and Mfn2, help to protect mitochondria from fusion defects caused by CMT2A mutations (Detmer and Chan 2007).

Fzo1 is an OM membrane protein (**Fig. 3**) regulated in the presence of ATP by yeast Mdm30 (Fritz *et al*. 2003; Escobar-Henriques *et al*. 2006). In contrast, yeast cells contain two isoforms of the IM protein Mgm1, which exist in a roughly stoichiometric state (**Fig. 3**). A membrane-bound long Mgm1 isoform is created upon cleavage by a matrix metalloprotease, with a shorter more soluble version generated upon secondary cleavage by the rhomboid-type protease Pcp1 (Esser *et al*. 2002; Herlan *et al*. 2003; McQuibban *et al*. 2003). Both Mgm1 isoforms are required for successful fusion with cells containing a mutation in *mgm1* (or *fzo1* for that matter) displaying a fragmented mitochondrial morphology with a loss of mitochondrial DNA (Hermann *et al*. 1998; Rapaport *et al*. 1998; Wong *et al*. 2000; Chen *et al*. 2003; Wong *et al*. 2003). Fzo1 (Mfn1/Mfn2) and Mgm1 act in *trans* to bring about mitochondrial fusion forming hetero- or homozygous complexes that tether the opposing outer/inner membranes respectively. GTP is required for the contraction of these complexes bringing the opposing membranes into contact for subsequent fusion (**Fig. 3**) (Koshiba *et al*. 2004; Meeusen *et al*. 2006).

The role of Mgm1 is not limited to IM fusion: it is also involved in the maintenance of mitochondrial cristae, primarily through its GTPase effector domain, with immunoelectron microscopy revealing that Mgm1 localises to the cristae both *in vitro* (Meeusen *et al*. 2006) and *in vivo* (Wong *et al*. 2000). These findings are supported by work on OPA1 where it was found that OPA1 regulates apoptosis by controlling cristal remodelling independent of mitochondrial fusion (Frezza *et al*. 2006), predominately through the soluble isoform of OPA1 (Cipolat *et al*. 2006).

It is interesting to note that while chloroplasts do not undergo organelle fusion as do mitochondria, they do utilise the Fzo-like protein FZL in a probable membrane tethering role – in the maintenance of thylakoid morphology (Gao *et al*. 2006). Plants with an *fzl* mutation show a slower growth rate and have mesophyll cells with fewer but larger chloroplasts; FZL-GFP fusions associate with both the thylakoid and chloroplast IM (Gao *et al*. 2006). FZL, with its Fzo-like structure, may be a key step in our understanding of the evolution of fusion proteins, and may provide clues to the evolution of Fzo proteins in mitochondrial fusion.

FULL CIRCLE: BACTERIAL DYNAMIN-LIKE PROTEINS

The lack of any obvious homolog of dynamins in the bacteria indicated that dynamin was a protein of eukaryotic origin. An exciting recent report of a bacterial dynamin-like protein (BDLP) from a filamentous cyanobacterium, questions the evolutionary origins of DLPs: the structure of BDLP has high similarity to the mitofusin DLPs, particularly FZL from *Arabidopsis* (Low and Löwe 2006). Bacterial dynamin-like protein localised in a pattern similar to that of FZL in plastids, with puncta at the cell periphery and in the cell interior (Low and Löwe 2006). Given the endosymbiotic ancestry that chloroplasts owe to cyanobacteria, it is possible that BDLP acts in determining thylakoid morphology and cell shape, similar to the role FZL plays in chloroplasts (Low and Löwe 2006). When these findings are taken in context with the knowledge that many eubacteria contain hypothetical genes encoding possible DLPs (van der Bliek 1999), it indicates that dynamins arose not from the eukaryotic host but from the endosymbiont, and that the dynamin super family is derived from a bacterial ancestor (Low and Löwe 2006). The early evolutionary origin of OM organelle constriction via DLPs (supported by the vast array of eukaryotes that utilise DLPs for chloroplast and mitochondrial OM constriction), supports a bacterial origin of DLPs. It is tempting to speculate that the diversity of the dynamin super family (Praefcke and McMahon 2004) arose from three separate adaptations of BDLPs: 1) BDLPs present in the original eukaryote host 2) BDLPs adapted from the mitochondrial α-proteobacterial ancestor and 3) BDLPs adapted from the chloroplast cyanobacterial ancestor. Further characterization of BDLPs, especially from relatives of cyanobacteria and α-proteobacteria, is clearly an area for fruitful research.

CONCLUDING REMARKS

Chloroplasts and mitochondria share many division mechanisms, most likely because of their shared endosymbiotic origins. Perhaps the greatest similarity is in the use of DLPs for final organelle severance. With our limited knowledge of the proteins involved, it is difficult to yet determine whether or not chloroplasts and mitochondria utilise similar proteins to recruit DLPs from the cytosol and anchor them to the OM. The mitochondrial recruitment apparatus in yeast consists of three interacting proteins Fis1, Mdv1 and Caf4, no homologs of which have been found that might act in plastid division. In terms of function however, Fis1 and PDV1/2 are quite similar. Both are targeted to their respective organelle OM with their C-termini in the IMS, recruiting DLPs facilitated via interactions at the N-terminus (in the case of Fis1 this is in concert with Mdv1). Further investigation of PDV1/2 will be required to fully understand their cellular functions, but it will be interesting to determine whether PDV1/2 plays a broader cellular role – similar to the way Fis1 not only recruits DLP but is involved in the apoptotic pathway.

While Mdv1 and Caf4 were thought to be unique to fungi, the discovery of Mda1 in *C. merolae* (Nishida *et al.* 2007) suggests that homologs of these proteins, or at least structural analogs of similar domain structure and function, may be more diverse than previously thought. The lack of sequence conservation in these proteins (even between species) makes identification of homologs in distantly related organisms difficult. Instead of relying on secondary sequence as a means of comparison and identification, we may have to search for structural analogs based upon domain comparisons using databases like OrthoMCL-DB (Chen *et al.* 2006) or crystal structures to uncover DLP recruitment homologs and their evolutionary relationships.

DLPs are required for final organelle severance and have been shown to associate with the outer PD ring (Yoshida *et al.* 2006). However MD rings have only been observed in a few organisms to date (Kuroiwa *et al.* 2006), raising the question as to how DLP brings about mitochondrial division in the absence of MD rings. Determining the proteins comprising PD and MD rings will go a long way to answering this question. An actin-like protein is one possible answer, as actin plays a regulatory role in mitochondrial division (de Vos *et al.* 2005).

Arabidopsis chloroplast and cell division are coordinated (Raynaud *et al.* 2005), with many proteins involved early in chloroplast division characterised, mainly due to the assistance of bacterial homologs, a situation not mirrored in mitochondria. With the exception of mt-FtsZ (and now, possibly, DLPs) no bacterial homologs have been characterised in mitochondrial division. Proteins involved in the early stages of mitochondrial division, such as the determination of the division site and the mechanics of IM division, remain to be elucidated, leaving many challenges for the future.

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