Biochimica et Biophysica Acta 1833 (2013) 150–161

Contents lists available at SciVerse ScienceDirect

Biochimica et Biophysica Acta

journal homepage: www.elsevier.com/locate/bbamcr

Review

# Recent advances into the understanding of mitochondrial fission ☆

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ARTICLE INFO

*Article history:*
Received 9 March 2012
Received in revised form 24 April 2012
Accepted 2 May 2012
Available online 10 May 2012

*Keywords:*
Mitochondrion
Fission
Dynamin related protein 1
Mff
MiD49
MiD51

ABSTRACT

Mitochondria exist as a highly dynamic tubular network, and their morphology is governed by the delicate balance between frequent fusion and fission events, as well as by interactions with the cytoskeleton. Alterations in mitochondrial morphology are associated with changes in metabolism, cell development and cell death, whilst several human pathologies have been associated with perturbations in the cellular machinery that coordinate these processes. Mitochondrial fission also contributes to ensuring the proper distribution of mitochondria in response to the energetic requirements of the cell. The master mediator of fission is Dynamin related protein 1 (Drp1), which polymerises and constricts mitochondria to facilitate organelle division. The activity of Drp1 at the mitochondrial outer membrane is regulated through post-translational modifications and interactions with mitochondrial receptor and accessory proteins. This review will concentrate on recent advances made in delineating the mechanism of mitochondrial fission, and will highlight the importance of mitochondrial fission in health and disease. This article is part of a Special Issue entitled: Mitochondrial dynamics and physiology.



## 1. Introduction

Mitochondria form a dynamic cellular network that is tailored to the energetic and metabolic requirements of the cell [1,2]. Alterations in the network can be seen in the wrapping of fused mitochondria at the base of the sperm flagellum, the tight packing of discrete mitochondria within cardiac myocytes, and the formation of highly fragmented networks during mitosis [3–6]. The morphology of the mitochondrial network within cells represents a delicate balance between fusion and fission events. Proteins involved in both the regulation and maintenance of mitochondrial morphology have crucial roles in maintaining the health of the cell [2,7].

Mitochondria are not made de novo. The majority of mitochondrial proteins are imported into the organelle, membranes expand through both phospholipid synthesis and transport from other organelles, and mitochondrial DNA replicates [1,8]. Like their bacterial ancestors, mitochondrial growth is accompanied by division. At a basic level, this process can be viewed as allowing for a population of the mitochondrial network to be correctly inherited by daughter cells. However, mitochondrial fission is also required for other processes including facilitation of organelle transport and turnover [9–12]. Unlike bacterial fission which occurs through a protein machinery undertaking internal constriction events [13], eukaryotic cells (except primitive algae) control mitochondrial fission from the cytosolic face of the organelle [2,14,15]. The master regulator of mitochondrial fission is a largely cytosolic member of the dynamin family of GTPases termed Drp1 (Dynamin-related protein 1) in mammals, Dnm1 (Dynamin 1-like protein) in yeast, and DRP3A/B (formerly known as ADL2a/b) in *Arabidopsis thaliana* [16–22]. Drp1 polymerises into spirals around mitochondria, and through GTP hydrolysis constricts the mitochondrion leading to membrane scission (Fig. 1A) [23–26]. Drp1 activity at the mitochondrial outer membrane is regulated by a variety of post-translational modifications (Table 1), and interactions with mitochondrial accessory and effector proteins (Fig. 1).

Mitochondrial fission is balanced by opposing fusion events. The principal purpose of mitochondrial fusion appears to be the mixing of contents between adjacent organelles, in order to maintain a homogenous mitochondrial network within the cell [27]. Mitochondrial fusion is initiated by hetero- and homo-oligomeric protein complexes being formed between adjacent mitochondria, thus tethering two different mitochondrial membranes [28–33]. Interestingly, the central components of the fusion machinery—Mitofusins (Mfn1 and 2, Fzo1 in yeast) and OPA1 in mammals (Mgm1 in yeast)—are also members of the dynamin superfamily responsible for fusion of the mitochondrial outer and inner membranes respectively [28,34–40]. Knockout of either Mitofusin results in highly fragmented mitochondria [28], whilst reduction or loss of fission components results in unbalanced mitochondrial fusion [41–47], highlighting the fact that mitochondrial morphology represents a balance between fusion and fission.

☆ This article is part of a Special Issue entitled: Mitochondrial dynamics and physiology.

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doi:10.1016/j.bbamcr.2012.05.002

## 2. Components of mitochondrial fission

### 2.1. Drp1—the master fission mediator

Drp1 is an ~80 kDa protein that forms higher order structures upon binding to membranes, but exists primarily as dimers/tetramers in the cytosol [18,48–51]. A smaller population of Drp1 is found on the mitochondrial surface, and may represent scission intermediates or remnant scission sites where Drp1 depolymerisation from the membrane is incomplete [18,23,52]. Like the classical endocytic Dynamin 1, Drp1 can self-assemble into spirals and use GTP hydrolysis to undergo conformational change [23,25]. In vitro analysis demonstrated that hydrolysis of GTP is sufficient for Drp1 to constrict and tubulate liposomes, before Drp1 dissociates into solution [23,25]. This indicates that Drp1 (or Dnm1) has the capacity to execute binding, constriction and release from membranes without the addition of other factors. However, as multiple membrane environments may be encountered within the cell, specificity in the way Drp1 acts must ensue. Thus, additional factors are involved in maintaining specificity and regulating the events by which Drp1 acts (discussed below).

The domain structure common to the dynamin superfamily of proteins includes an amino terminal GTPase domain, a middle domain, and a GTPase effector domain (GED) (Fig. 2A) [16,18,25,53]. The recently solved structure of Dynamin 1, which is involved in endocytosis, has given clues into how Dynamin and dynamin-related proteins like Drp1 may function in membrane constriction and fission [54,55]. Dynamin 1 also includes a pleckstrin homology (PH) domain between the middle domain and the GTPase effector domain and a proline-rich C-terminal domain (PRD) (Fig. 2A) [54,55]. The crystal structure of near full-length Dynamin 1 (lacking only the C-terminal proline-rich domain) reveals a hairpin-like structure where flexible disordered linkers either side of the PH domain allow the formation of a helical stalk comprised of the middle and GTPase effector domains [54,55]. The GTPase domain forms the "head" of the stalk which sits on a "neck" region known as the bundle signalling element (BSE) (Fig. 2A) [54–56]. The BSE is formed from three helices derived from sequences at the N- and C-terminal sides of the GTPase domain and a sequence C-terminal to the GTPase effector domain [54–56]. The PH domain forms the "foot" of the structure and binds phosphoinositides, which may help to scaffold the structure along the membrane surface [54,55,57–60] and alter lipid composition at constriction sites [61]. Interaction between Dynamin 1 monomers is proposed to occur via the stalk region forming cross-like head to foot dimers (Fig. 2B), with polymerisation occurring through interactions between the stalks of adjacent dimers forming a helical assembly observable through cryo-EM [54,55]. Dynamin 1 GTPase domains in adjacent rungs of the helix are able to interact in a GTP-dependent manner [54,55]. Formation of this structure is thought to stimulate GTPase activity, with the resultant hydrolysis of GTP creating a conformational change in the "neck" region causing constriction of the helix in a ratchet-like manner and ultimately membrane fission (Fig. 2B) [54–56]. A similar GTP-dependent helical assembly has also been observed for Dnm1, however Dnm1 forms a 2-start helix

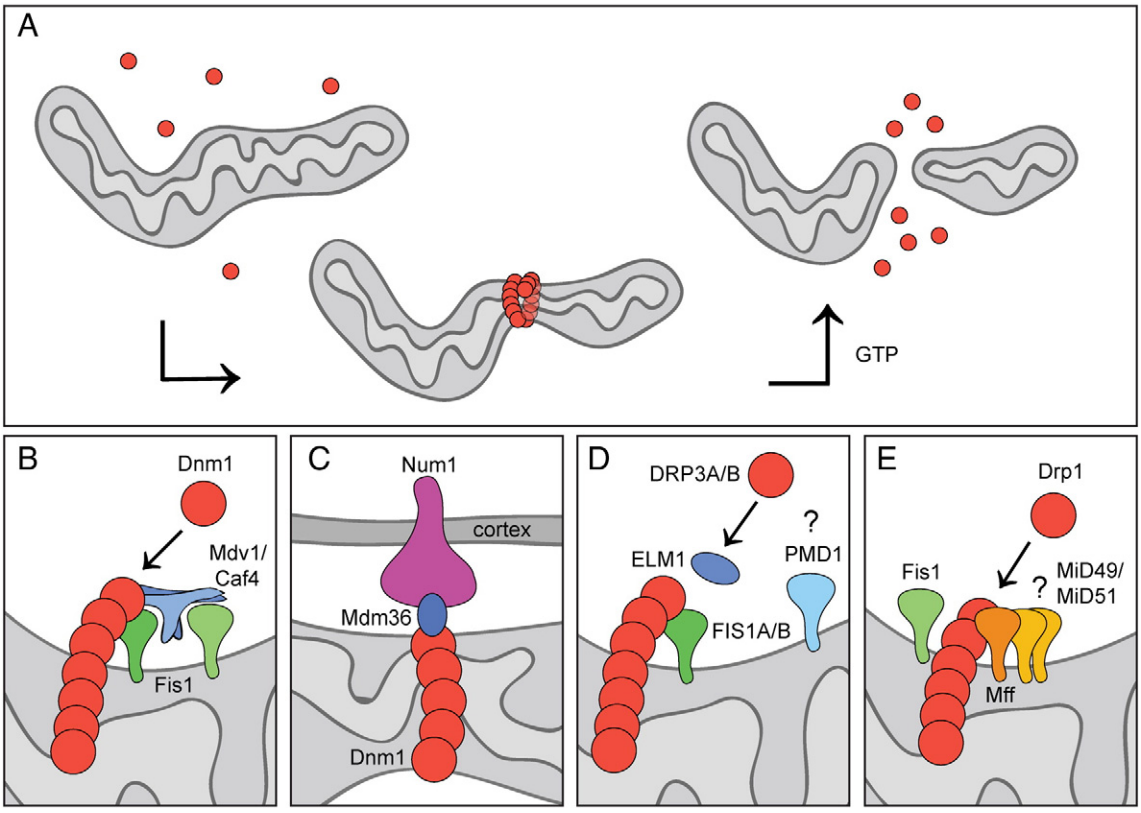


**Fig. 1.** Mitochondrial fission in yeast, plant and mammalian cells. (A) The current models of mitochondrial fission in yeast and mammalian cells share the involvement of the master fission mediator Drp1/Dnm1. Drp1 oligomerises into spirals around mitochondria at future fission sites, constricting and subsequently dividing the mitochondrion through GTP hydrolysis. (B) In yeast, Fis1 interacts with dimers of the adaptor proteins Mdv1 (or Caf4) forming a platform for Dnm1 recruitment. (C) A second fission complex in yeast may involve mitochondrial located Dnm1 anchored at the cell cortex by the yeast accessory proteins Mdm36 and Num1, which causes membrane tension to facilitate the scission event. (D) Mitochondrial fission in plants is mediated by the Drp1 homologue DPR3A/B. DRP3 associates with the outer mitochondrial membrane receptors FIS1A/B. This interaction is potentially mediated by the plant specific protein, elongated mitochondria 1 (ELM1). The peroxisomal and mitochondrial division 1 (PMD1) may also have a role in fission independent of FIS and DRP3. (E) Mammalian mitochondrial fission is mediated by outer membrane receptors (including Fis1, Mff and MiD49/51) that are proposed to act in the recruitment and association of Drp1 with mitochondria.

**Table 1**
Regulation of Drp1 activity through post-translational modification.

| Post-translational modification | Residue | Modifying protein | Effect | Reference |
|---|---|---|---|---|
| Phosphorylation | Ser 616 (Ser585 in rat) | Cyclin B dependent kinase (CDK1) | Mitochondrial fragmentation during mitosis | [95,115] |
| Phosphorylation | Ser637 (Ser656 in rat) | Cyclic AMP-dependent protein kinase (PKA) | Inhibition of Drp1 GTPase activity and inhibition of mitochondrial fission | [96,97] |
| Phosphorylation | Ser600 (Ser637 human splice variant) | Calcium/calmodulin-dependent kinase Iα (CaMKIα) | Increased affinity for Fis1, stimulation of mitochondrial fission | [98] |
| Phosphorylation | Ser600 | Rho-associated coiled coil-containing protein kinase 1 (ROCK1) | Stimulation of mitochondrial fission during hyperglycemia | [111] |
| Dephosphorylation | Ser637 | Calcineurin | Promotes Drp1 translocation to mitochondria and mitochondrial fission | [97,99] |
| *S*-Nitrosylation (SNO) | Cys644 | β-Amyloid | May enhance GTPase activity and Drp1 oligomer formation in Alzheimer's disease; may stimulate Drp1 phosphorylation at Ser616 | [101,102,202] |
| Ubiquitination | – | MARCH5/MITOL | Regulates the kinetics of Drp1 binding to the mitochondria | [103,104,106] |
| Ubiquitination | – | Parkin | Proteasome-dependent degradation of Drp1 | [105] |
| SUMOylation | – | Mitochondrial-anchored protein ligase (MAPL) | Stimulates mitochondrial fission and Drp1 stable association with mitochondria (stimulated by Bax/Bak) | [86,109,110] |
| DeSUMOylation | – | Sumo protease SENP5 | Stimulates mitochondrial fragmentation during mitosis, enhanced Drp1 cycling | [108] |

where the dynamin 1 helix contains a single start helix [25]. The magnitude of constriction of the Dnm1 helix is also greater than that of dynamin [25], allowing for constriction of the mitochondrial double membrane. Interestingly, Drp1/Dnm1 does not possess a conserved PH domain as found in dynamin 1 [53]. Whilst some residues of the PH domain are conserved in a PH-like domain (termed B insert or variable domain), the central helix involved in lipid interaction is not, and loss of this PH-like domain does not prevent in vitro association of Drp1 with liposomes [62]. In fact, the increased magnitude of constriction demonstrated by Dnm1 may be facilitated by both the flexibility of the helical assembly (as demonstrated in the Dynamin 1 structure), and the capacity of the helix to slide over lipids during constriction [25,54,55]. Whilst the PH domain of Dynamin 1 mediates association with phospholipids, the variable domain of Drp1 may influence association with mitochondrial receptor proteins (Fig. 2C) [25,57–59]. In addition, Drp1 orthologue and tissue-specific isoforms harbour different sequences and inserts [53]. This may account for the existence of different accessory factors that are required to recruit Drp1 and Dnm1 to mitochondria.

The physiological importance of mitochondrial fission has been demonstrated by the identification of a patient with a dominant negative mutation in Drp1 [44]. The patient exhibited a broad range of abnormalities including poor brain development, optic atrophy, and lactic acidemia, with mortality occurring at 37 days post gestation [44]. In addition, using mouse gene knockout models, Ishihara et al. [42] and Wakabayashi et al. [43] independently found that loss of Drp1 results in embryonic lethality, with death recorded in utero at E10.5–E12.5 [42,43]. Similar results were reported for the recently described "Python" mouse, with a middle domain mutation in Drp1 (C452F) resulting in embryonic lethality by E12.5 [63]. Specific defects in placental cell development were observed in *Drp1*$^{-/-}$ embryos with the trophoblast giant cell layer missing [43]. Strikingly, this defect was also observed in Mfn2 null mice pointing to a critical role in fission–fusion processes in placental development [28]. The main developmental abnormalities observed in Drp1 knockout mice were defects in forebrain and synapse development, poorly developed livers, and compromised cardiac formation or function [42,43], whilst the heterozygous Python mouse exhibited depletion of cardiac ATP and cardiomyopathy [63]. Interestingly, *Drp1*$^{-/-}$ mouse embryonic fibroblasts (MEFs) were viable and found to have elongated mitochondria and peroxisomes, yet mitochondrial function appeared normal [42,43]. The mitochondrial network in *Drp1*$^{-/-}$ MEFs did not fragment during mitosis like control cells, however cytokinesis still occurred with a population of mitochondria inherited by daughter cells (although possibly unequally) [42]. The constriction of the plasma membrane and the shearing stresses placed at the cleavage furrow during mitosis may be sufficient to induce mitochondrial fission, acting as a surrogate for Drp1, suggesting that Drp1-dependent mitochondrial fission is not essential for cellular division. Aggregation and improper distribution of mitochondria observed in *Drp1*$^{-/-}$ neurites, and increased sensitivity to apoptosis within neuronal cells, are likely due to impaired ATP supply and/or calcium buffering at specific regions within the cell [42]. The dependence of Drp1 mediated mitochondrial fission within cardiac development and function may also be due to abrogated ATP supply within cells with high energy demands, although the precise role of Drp1 in heart function is still under investigation [42,43,63].

### 2.2. Yeast accessory proteins

In yeast, Dnm1 recruitment and assembly at mitochondria are mediated by the membrane receptor Fis1 and the adaptor proteins Mdv1/Caf4 (Fig. 1B) [16,17,64–68]. Fis1 is localised to both mitochondrial and peroxisomal outer membranes, and peroxisomal fission is driven by a common mechanism also involving Dnm1 and Mdv1 [69,70]. Structural analysis of yeast Fis1 revealed the presence of a tetratricopeptide repeat-like domain, which is commonly involved in protein–protein interaction [71,72]. Recent structural analysis has shown that Mdv1 dimerises by forming an anti-parallel coiled-coil that sandwiches between the concave surface of two Fis1 molecules [65,73]. The Fis1–Mdv1 scaffold promotes the assembly of Dnm1, and stimulates Dnm1 polymerisation and subsequent constriction of the mitochondrial membrane [23,24,48]. The C-terminus of Mdv1 mediates the interaction with Dnm1 through a predicted WD-40 β-propeller domain [74,75].

Recently the yeast accessory proteins Num1 and Mdm36 were found to interact with Dnm1 to mediate mitochondrial fission, adding further complexity to the mechanism of mitochondrial division in this organism (Fig. 1C) [76,77]. Deletion of either Num1 or Mdm36 results in the formation of a fused mitochondrial network, similar to Dnm1 deletion mutants [76,77]. It has been suggested that Num1 and Mdm36 interact with Dnm1 to anchor mitochondria at the cell cortex in concert with actin, facilitating mitochondrial division through membrane tension [76,77]. In addition, the interaction of Num1 with mitochondria occurs independently of Fis1 [76]. Taken together, these studies demonstrate the formation of two Dnm1-fission complexes—a Dnm1/Mdv1/Fis1 complex, and a complex containing

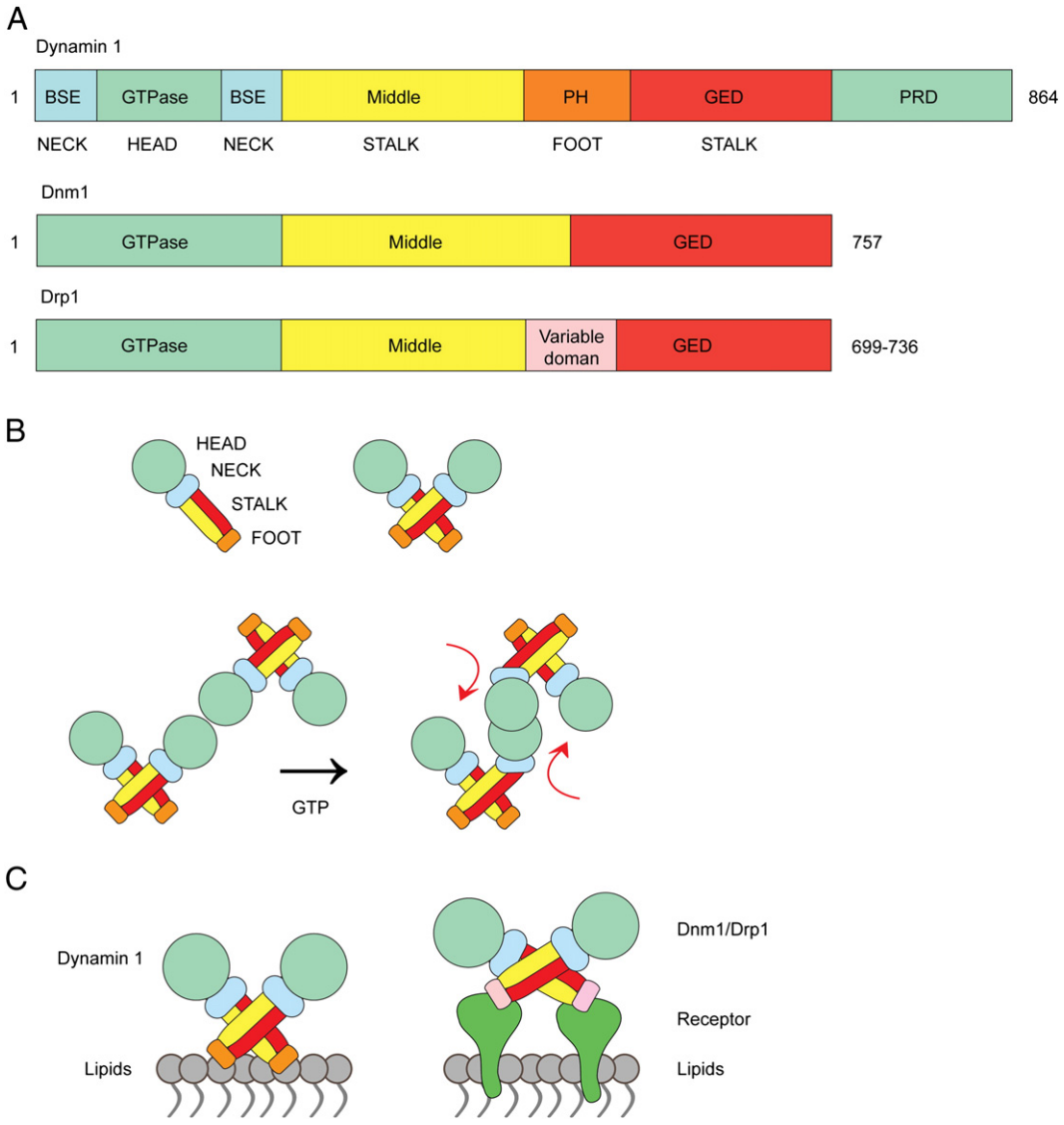


**Fig. 2.** Domain structure and assembly of Dynamin 1 and Drp1/Dnm1. (A) Dynamin 1 contains a GTPase domain, a middle domain, a pleckstrin homology (PH) domain, a GTPase effector domain (GED) and a proline rich domain (PRD). The GTPase domain is flanked by the bundle signalling elements (BSE). Dnm1 and Drp1 contain GTPase domains, middle domains and GED domains. Drp1 also contains a variable domain. Dnm1/Drp1 do not possess PH or PRD domains. (B) Dynamin 1 forms a hairpin-like structure, with the GTPase domain forming the head, the BSE forms the flexible neck, and the middle and GED domains form the stalk. The head domains of adjacent helices interact, with constriction stimulated by GTP hydrolysis and subsequent conformational change of the neck region. (C) The PH domain of Dynamin 1 inserts into the lipid bilayer and facilitates interaction with phospholipids to anchor the Dynamin helix and facilitate membrane scission. The variable domain of Dnm1/Drp1 does not interact with the lipid bilayer, but may facilitate interaction with mitochondrial outer membrane receptor proteins.

Dnm1/Num1/Mdm36. The mechanisms regulating the formation of these specific protein complexes are currently unknown.

### 2.3. Accessory proteins in plants

In plants, DRP3A/B recruitment to mitochondria and peroxisomes is mediated by the Fis1 homologues FIS1A/B (Fig. 1D) [78,79]. FIS1A/B are dual targeted to both mitochondria and peroxisomes as seen with Fis1 in yeast and mammalian systems, however these homologues are partially redundant in mitochondrial fission [79]. Whilst both DRP and FIS1 plant isoforms are active in mitochondrial fission, DRP3A and FIS1B have prominent roles in peroxisome fission, suggesting that these isoforms may regulate peroxisomal fission independently [80,81]. Whilst there are no homologues of Mdv1/Caf4 in plants, the association of DRP3 with FIS1 may be regulated by the mitochondrial associated protein elongated mitochondria1 (ELM1) [82]. *Arabidopsis* ELM1 mutants exhibit mitochondrial elongation similar to that of FIS1 and DRP3A mutants, and loss of ELM1 prevents DRP3A localisation to mitochondria, suggesting a role for this protein in DRP3 mediated mitochondrial fission [82]. Whilst no interaction between DRP3 or FIS1 and ELM1 has been demonstrated, it has been suggested that this protein may mediate the association of DRP3A/B with FIS1A/B as seen with Mdv1/Caf4 [82]. The recently identified peroxisomal and mitochondrial division factor1 (PMD1) has also been identified to have a role in mitochondrial and peroxisomal fission and biogenesis in plants [83]. PMD1 is a C-terminal tail anchored protein that is localised to both peroxisomes and mitochondria, whilst the homologue PMD2 is localised exclusively to the mitochondrial outer membrane [83]. PMD1 null mutants exhibit elongated mitochondria and peroxisomes, with over-expression resulting in increased mitochondrial and peroxisomal proliferation [83]. PMD1 and PMD2 can form both homo and hetero complexes, however no interaction between these proteins and the current division machinery has been established [83]. Whilst PMD1 may be active in proliferation of peroxisomes and mitochondria, PMD1/2 may also have a role in mitochondrial fission that is independent of FIS1 and

DRP3, or may interact with downstream effector proteins that have yet to be identified.

### 2.4. Accessory proteins in higher eukaryotes

Initial models of mammalian mitochondrial fission were based on findings from yeast, with Fis1 proposed as the main Drp1 receptor protein. Overexpression of human Fis1 induces mitochondrial fragmentation in mammalian cells, whilst knockdown leads to the formation of mitochondrial extensions [41,84]. More recently, Otera et al. [45] demonstrated that mitochondrial morphology was unaffected in colorectal carcinoma HCT116 Fis1$^{-/-}$ cells. Furthermore, Drp1 association with mitochondria was not disrupted in these Fis1 knockout cells [45], as seen previously following targeted knockdown of Fis1 [85,86]. The lack of mammalian homologs of Mdv1/Caf4 also suggests that there are other proteins regulating Drp1 association with mammalian mitochondria. Concordantly, several novel Drp1 recruiting proteins have been identified including Mitochondrial Fission Factor (Mff) and the Mitochondrial Dynamics proteins MiD49 and MiD51 (also termed MIEF1) (Fig. 1E) [45,47,87,88].

#### 2.4.1. Mitochondrial Fission Factor, Mff

Despite the homology between yeast and mammalian Fis1 and Drp1, increasing evidence suggests that these two proteins do not act in the same fission pathway in mammalian cells. Recently, Mitochondrial Fission Factor (Mff) was found to recruit Drp1 to mitochondria independently of Fis1 [45,87]. Mff is anchored in the mitochondrial outer membrane at its C-terminal end with the majority of the protein projecting into the cytosol [45,87]. Mff is conserved from *Caenorhabditis elegans* to humans and contains two short N-terminal repeats that have been suggested to act as a binding site for Drp1, potentially acting in similar fashion to the WD-40 repeats in Mdv1 [45,87]. Mff also contains a central coiled-coil domain that is required for correct targeting of the protein [45]. Knockdown of Mff by RNA interference induces mitochondrial elongation and reduces Drp1 association with mitochondria [45]. Conversely, Mff overexpression induces Drp1 recruitment and increased mitochondrial fission [45]. Mff was found to transiently interact with Drp1 via its cytosolic domain, whilst fluorescence microscopy demonstrated colocalisation of Drp1 and Mff at discrete sites on the mitochondrial surface [45,87]. However the association appears to be transient, since chemical cross-linking was required for their co-immunoprecipitation [45]. Immunoprecipitation experiments revealed that Drp1 associates with Mff, with a higher affinity than Fis1 [45], suggesting that Mff preferentially functions as a Drp1 receptor. In addition, Mff and Fis1 exist in separate 200-kDa complexes, suggesting that they do not operate in the same fission pathway in mammalian cells [45].

#### 2.4.2. Mitochondrial Dynamics proteins—MiD49 and MiD51

Recently two additional proteins were found to recruit Drp1 to the mitochondrial surface. Mitochondrial Dynamics proteins of 49 and 51 kDa (MiD49 and MiD51 respectively) are orthologous at the sequence level, are N-terminally anchored in the mitochondrial outer membrane and are largely exposed to the cytosol [47]. At low level expression, MiD49/51 are found at discrete foci and form apparent rings around mitochondria, similar to that observed for Drp1 [26,47,52]. Following high level overexpression of MiD49 or MiD51, mitochondria become highly fused whilst paradoxically, Drp1 shifts to mitochondria [47]. Live cell imaging shortly after induction of MiD51 expression revealed that Drp1 is initially recruited to mitochondria and can induce mitochondrial fission [47]. At later stages when the mitochondrial network became more fused, it was suggested that Drp1 becomes sequestered at mitochondria in a non-functional form, thereby blocking fission and shifting the balance towards fusion [47]. Like Mff, an interaction between MiD49/51 and Drp1 could be seen following chemical crosslinking experiments [47]. Shortly after the publication by Palmer et al. [47], MiD51 was independently identified as Mitochondrial Elongation Factor 1 (MIEF1) [88]. Zhao et al. [88] also found that overexpression of MiD51/MIEF1 leads to mitochondrial recruitment of Drp1, and the formation of elongated mitochondria [47,88]. However following knockdown of both MiD49/51, Palmer et al. [47] observed decreased levels of Drp1 at mitochondria and a more extended network, whereas Zhao et al. [88] observed fragmentation of mitochondria upon knockdown of MiD51 alone. Fis1 was also demonstrated to interact with MiD51/MIEF1, and it was suggested that the interaction of MiD51/MIEF1 with Fis1 and Drp1 acts to block mitochondrial fission. However the authors also suggest that MIEF1 promotes mitochondrial fusion independent of Mitofusins [88]. Whilst both studies demonstrate an association of MiD51/MIEF1 with Drp1, the differences observed upon knockdown suggest alternate interpretations of function in either mitochondrial fission or fusion. Clearly, further studies to clarify the role of MiD49 and MiD51/MIEF1 in mitochondrial morphology are required.

#### 2.4.3. Fission accessory proteins MTP18, GDAP1, and Endophilin B1

Additional proteins involved in mitochondrial fission are MTP18, a mitochondrial protein of 18 kDa [46,89] and GDAP1 (Ganglioside-induced differentiation-associated protein 1) [90–92], located in the inner and the outer mitochondrial membranes respectively. Both proteins have been shown to induce fusion of the mitochondrial network upon knockdown and fragmentation upon overexpression [46,89,91]. MTP18 induced mitochondrial fragmentation is mediated by Drp1 [46], but further characterisation of both proteins and their role in mitochondrial fission is missing. Endophilin B1 is thought to be involved in lipid remodelling of the outer mitochondrial membrane [93]. Most of the Endophilin B1 in the cell is cytosolic but a fraction is associated with mitochondria [93]. However, upon induction of apoptosis, Endophilin B1 is activated by the pro-apoptotic protein Bax, suggesting its involvement in remodelling of the mitochondrial membrane during apoptosis [93,94].

## 3. Regulation of mitochondrial fission

Drp1 is post-translationally modified by phosphorylation [95–100], *S*-nitrosylation [101,102], ubiquitination [103–107] and SUMOylation [86,108–110] (Fig. 3, Table 1). These modifications can change the localisation, dynamics and activity of Drp1. Interestingly, the phosphorylation status of Drp1 on different amino acid residues can cause opposing effects (Table 1) [95–99]. Phosphorylation of Drp1 by Calcium/calmodulin-dependent protein kinase 1α at Ser600 (or Ser637 on a human drp1 splice variant; Ser656 in rat Drp1) increases Drp1 translocation to mitochondria and association with Fis1 in mammalian cells [98]. Phosphorylation of Drp1 by the serine/threonine kinase ROCK1 at the same residue in response to hyperglycemic stimulation also results in Drp1 translocation to mitochondria, and increased mitochondrial fission [111]. In contrast, cAMP-dependent protein kinase phosphorylation of Drp1 at the same residue inhibits Drp1 activity [96,100], whilst Drp1 dephosphorylation by calcineurin stimulates Drp1 translocation to mitochondria [99]. This variation in Drp1 activity upon phosphorylation may depend on external parameters such as cell type, age or status, or on internal parameters such as the localisation of Drp1. It is also likely that these kinases phosphorylate/dephosphorylate multiple protein targets, further complicating the interpretation of role of Drp1 phosphorylation in mitochondrial fission.

Inheritance of mitochondria by daughter cells during mitosis is essential to ensure the viability of the newly produced cells, and is facilitated by extensive fragmentation of the mitochondrial network followed by distribution of the individual segments [95,108]. Aurora A is a mitotic kinase that localises to the centrosome at different phases of mitosis [112,113]. It is associated with centrosome

maturation and separation, and regulates spindle assembly and stability [112–114]. Kashatus et al. [115] demonstrated that following Aurora A mediated phosphorylation of the small Ras-like GTPase RALA, a portion of RALA and its effector RALBP1 moves from the plasma membrane to mitochondria, or vesicles associated with mitochondria. Concordantly, RALBP1 is proposed to act as a scaffold for cyclin B-CDK, subsequently promoting phosphorylation of Drp1 and mitochondrial fission [95,115]. The mitotic fission process also involves Mff, as knockdown of Mff decreased the recruitment of both RALBP1 and Drp1 to mitochondria at mitosis, whilst Fis1 knockdown did not [115]. The role of additional factors (including MiD49/51) in mitochondrial fission during mitosis remains to be established.

The role of ubiquitination in the regulation of Drp1 is still a matter of conjecture. Ubiquitination of Drp1 is mediated by the E3 ligases MARCH5 (also known as MITOL) and Parkin [103–106,116]. It has been proposed that MARCH5 regulates mitochondrial fission by a ubiquitin mediated switch [103]. Silencing of MARCH5 and overexpression of MARCH5 mutants have been reported to induce mitochondrial fragmentation or elongation, as well as abnormal mitochondrial accumulation of Drp1 [103,104,106]. Subsequently, the role of MARCH5 in mitochondrial fission remains to be clarified. Ubiquitination of Drp1 by the E3 ligase Parkin targets it for degradation by the proteasome [105]. A number of proteins involved in mitochondrial morphology have recently been identified as targets of Parkin mediated degradation [105,117]. Drp1 is also post-translationally modified by the small ubiquitin-like modifier (SUMO) [86,110]. SUMOylation of Drp1 occurs at multiple sites and is proposed to stimulate the stable association of Drp1 with mitochondria during apoptosis, and influence Drp1 activity [86,110]. DeSUMOylation of Drp1 by the SUMO protease SenP5 during mitosis increases the pool of Drp1 available for mitochondrial fission, facilitating fission during mitosis [108].

## 4. Interaction between proteins of the fusion and the fission machinery

Fission and fusion are inextricably linked. Using live cell imaging, it has been elegantly shown that the sites of mitochondrial scission can similarly act as sites of fusion [10]. In addition, mitochondrial fusion can be rapidly followed by a fission event [118,119]. Direct interactions between components of the fusion and fission machinery have also been reported. Mfn2 contains two heptad-repeat regions (HR1 and HR2) that can either interact with the HR region of another Mfn protein actively promoting mitochondrial fusion, or interact with each other resulting in inhibition of fusion [120]. In addition, the two heptad-repeat regions of Mfn2 can also interact with the C-terminal coiled-coil domain of the fission protein Drp1 [120]. This suggests that the Mfn2/Drp1 interaction actively promotes mitochondrial fusion. Thus, Drp1 might function as a regulatory factor for efficient execution of both fusion and fission of mitochondria. Similarly, the Bcl-2-like protein CED-9 has been shown to physically interact with Mitofusin and Drp1 counterparts (FZO-1 and DRP-1) in *C. elegans* [121–123]. Previous studies in *C. elegans* and mammalian cells have demonstrated that Bcl-2-like proteins may promote mitochondrial fusion or fission, depending on the physiological context [122–127]. The interaction of CED-9 with Drp1 can be enhanced when CED-9 is associated with the BH3-only protein EGL-1 [121]. The EGL-1–CED-9 complex actively promotes mitochondrial fission by recruiting Drp1 to mitochondria, suggesting that EGL-1 shifts CED-9 from a pro-fusion to pro-fission role by converting it into a mitochondrial receptor for Drp1 [121]. In mammalian cells, activation of apoptosis stimulates Drp1 recruitment to mitochondria, where it is proposed to co-localise with Bax and Mfn2 foci [86,128]. The soluble non-apoptotic form of Bax regulates mitochondrial fusion through interaction with the Mitofusins, and the formation of Mfn2 homotypic complexes [125,127,129]. Bax and Bcl-xL have also been shown to interact with Mfn1/Mfn2 and Drp1 in mammalian cells, regulating mitochondrial morphology through inhibition of mitochondrial fusion and stimulation of fission [124,127]. Interactions between proteins of the fusion and the fission machinery may indicate self-regulatory feed-back mechanisms via inhibitory or activating effects on mitochondrial morphology proteins. Alternately, it may be that the Bcl-2 family members act as biological switches that regulate rates of mitochondrial fission. The precise nature of this regulation remains to be explored.

## 5. Apoptosis and necroptosis

Mitochondria are involved in the intrinsic apoptotic pathway, and Drp1-dependent mitochondrial fragmentation and cristae remodelling have long been linked to apoptosis in mammals [130–133]. Mitochondria undergo extensive fragmentation during apoptosis concomitant with mitochondrial outer membrane permeabilisation (MOMP) and cytochrome *c* release [133–135]. Inhibition of mitochondrial fission by down regulation of Fis1, Drp1 or Mff has been shown to delay cytochrome *c* release, suggesting that mitochondrial fusion is protective against apoptotic insult [85,87,136,137]. Under apoptotic stimulation, Fis1 and Drp1 associate with lipid raft-like domains at mitochondria, with chemical disruption of these rafts impairing mitochondrial fission and apoptosis [138]. These raft-like domains may act as platforms for recruitment of Drp1 and mitochondrial lipid modifications during apoptosis. However, whilst Drp1 knockout or down regulation delays cytochrome *c* release, it fails to prevent release of other cofactors that induce caspase activation and subsequent apoptosis [42,43,136], suggesting that Drp1-dependent mitochondrial fragmentation is not a prerequisite for apoptosis. Other studies have also shown that fission is neither essential for cytochrome *c* release nor obligatory for apoptosis, indicating that these are separate events [139,140]. In addition, restoration of the mitochondrial network following inhibition of Drp1 in lung cancer cells has been shown to induce spontaneous apoptosis [141], further confusing the role of mitochondrial fission in apoptosis. Fragmented mitochondria show enhanced sensitivity to Bax insertion and activation during apoptosis [142]. Brooks et al. [142] suggested this may be due to changes in the biophysical properties of the mitochondrial membrane as a result of changes in membrane curvature or lipid composition at fission sites simplifying the docking and insertion of Bax into the membrane. Bax/Bak have also been shown to colocalise with Drp1 and Mfn2 during apoptosis, stimulating Drp1 SUMOylation and stable association with the mitochondrial outer membrane [86,128].

A connection between mitochondria and the endoplasmic reticulum (ER) in calcium signalling and apoptosis has long been known. The association of mitochondria with the ER is important for the transfer of phospholipids and calcium [143–145]. This association occurs through specific regions of the ER termed the mitochondria-associated membrane (MAM) [146]. The ER can help initiate necrosis/apoptosis by the release of calcium, which is then rapidly taken up by proximal mitochondria [147–149]. Accumulation of calcium in the mitochondrial matrix can lead to cell death, as calcium interacts with cyclophilin D to induce opening of the mitochondrial permeability transition pore (MPTP), which is regulated by Bcl-2 family proteins such as Bak and Bax [147,150–152]. Opening of the MPTP leads to matrix swelling, rupture of the mitochondrial outer membrane and subsequent cytochrome *c* release [150,153]. The precise mechanism that regulates transfer of the apoptotic signal from the ER to mitochondria or vice versa remains to be delineated, however recent evidence suggests that ER–mitochondrial communication during apoptosis involves Fis1 and Drp1. Fis1 can transfer the apoptotic signal from the mitochondria to the ER by forming a complex with the ER-located protein Bap31 at the ER–mitochondria interface [154]. The Fis1–Bap31 complex, called the 'ARCosome', forms a platform for the recruitment and activation of procaspase-8, an early event during apoptosis induction [154]. Following Bap31 cleavage and release of calcium stores from the ER, Drp1 is recruited to mitochondria followed by mitochondrial

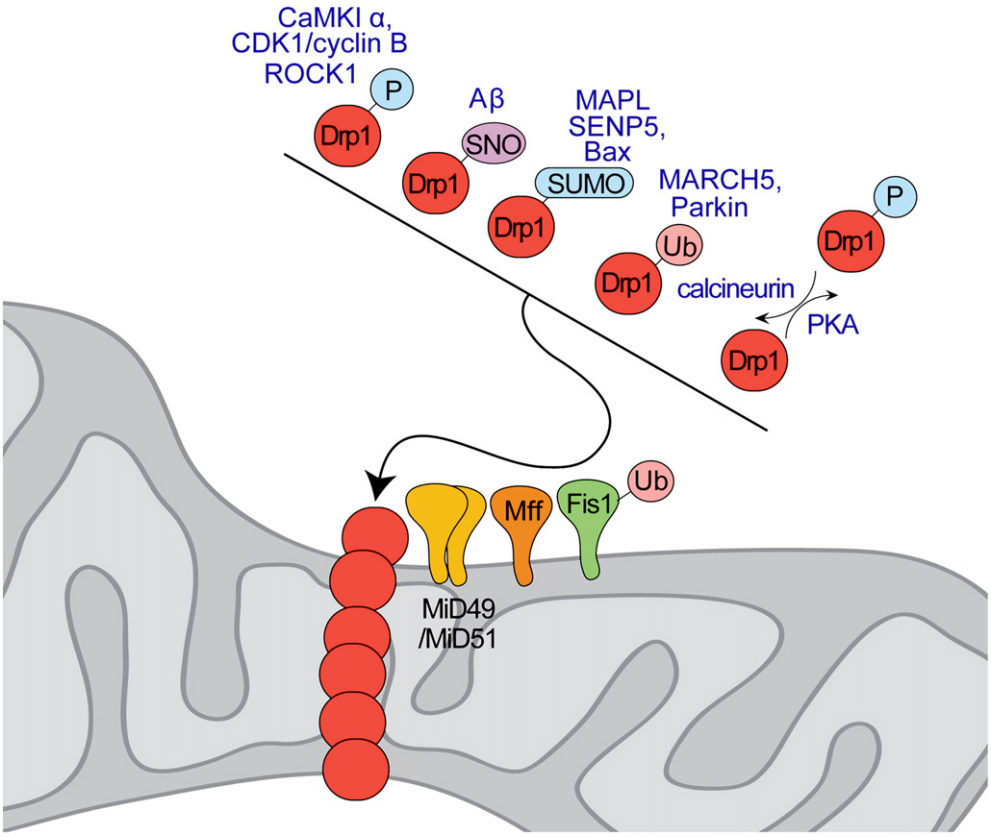


**Fig. 3.** Mitochondrial morphology is influenced via posttranslational modification of Drp1. Drp1 undergoes reversible processes of SUMOylation, ubiquitination, *S*-nitrosylation or phosphorylation mediated by different regulatory proteins. These posttranslational modifications influence localisation, dynamics and activity of Drp1 thus enhancing or suppressing Drp1-mediated mitochondrial fission according to the cellular requirements. Mitochondrial fission is stimulated upon phosphorylation of Drp1 by cyclin dependent kinase 1 (CDK1/cyclinB), $Ca^{2+}$/calmodulin dependent protein kinase 1α (CaMKIα), Rho-associated coiled coil-containing protein kinase 1 (ROCK1), and dephosphorylation by calcineurin. In contrast, Drp1 phosphorylation by cAMP-dependent protein kinase (PKA) inhibits mitochondrial fission. SUMOylation of Drp1 by mitochondrial-anchored protein ligase (MAPL) stimulates mitochondrial fission, whilst deSUMOylation by sentrin-specific protease 5 (SENP5) induces mitochondrial fission during mitosis. Bax has also been found to stimulate Drp1 SUMOylation. Drp1 and Fis1 are ubiquitinated by the E3 ligases MARCH5 and Parkin, with MARCH5 regulating Drp1 binding kinetics with mitochondria, and Parkin stimulating Drp1 proteasomal degradation. β-Amyloid (Aβ) may stimulate Drp1 *S*-nitrosylation (SNO), promoting mitochondrial fission.

fission and cytochrome *c* release [155]. Independently of Bap31 cleavage, ER localised BIK has also been shown to stimulate calcium mediated apoptosis, resulting in Drp1-dependent mitochondrial fission and cytochrome *c* release [156].

Recently, the group of Xiaodong Wang reported a connection between programmed necrotic cell death (necroptosis) and mitochondrial fission. They found that a short isoform of the mitochondrial phosphatase PGAM5 (PGAM5S) became activated by both external (TNFalpha) or internal (calcium ionophores, oxidative stress) signals that trigger necrotic cell death [157]. Activation of PGAM5S leads to dephosphorylation of Drp1 at Ser637 and its recruitment to mitochondria, activating Drp1GTPase activity and stimulating mitochondrial fission [157]. Significantly, when Drp1 is chemically inhibited or depleted by RNAi, necrosis is inhibited [157]. The question of how Drp1 and mitochondrial fission function in necrosis remains unanswered. Whilst mitochondrial fragmentation also occurs during apoptosis, the two events lead to different end points since apoptosis leads to cytochrome *c* release and caspase activation, whilst necrosis does not. It is therefore likely that other events are involved in mitochondrial fission during apoptosis and necrosis, and points to a deeper mechanism of regulation at mitochondria.

## 6. Mitochondrial constriction and the ER

A key finding about ER–mitochondrial contacts was made by de Brito et al. [144] who reported that Mfn2 is involved in tethering mitochondria to the ER. Loss of Mfn2 disrupts ER–mitochondrial contacts and subsequent calcium uptake by mitochondria [144]. This ER–mitochondrial association is negatively regulated by the cytoskeletal binding protein Trichoplein/mitostatin (TpMs) in a Mfn2 dependent manner, providing evidence of cytoskeletal assisted scaffolding [158]. Knockdown of TpMs by RNAi led to inhibition of calcium mediated apoptosis and mitochondrial elongation, whilst overexpression of TpMs resulted in mitochondrial fragmentation and reduced ER tethering to mitochondria [158]. Friedman et al. recently identified a role of the ER in mitochondrial morphology. ER tubules were shown to wrap around mitochondria at prospective fission sites, mediating constriction of the mitochondrial membranes and reducing the mitochondrial diameter by ~30% prior to Drp1 recruitment [159]. ER constriction of mitochondria was mainly observed at positions of Mff and Drp1 foci [159]. However, Drp1, Mff or Mfn2 knockdown did not affect ER–mitochondrial contacts, indicating that ER-mediated constriction of mitochondrial tubules is independent of these proteins [159]. Based on their results, Friedman et al. [159] suggest that ER proteins are actively involved in mitochondrial fission and/or ER tubules constrict mitochondria and act as a scaffold for Drp1 recruitment [159].

## 7. Mitochondrial fission and autophagy

Mitochondrial fission can result in the formation of healthy fusion-competent daughter mitochondria, or in the generation of unequal daughter mitochondria exhibiting differences in mitochondrial membrane potential, respiratory function and containing little or no mtDNA [10,160–162]. Mitochondria with a reduced membrane potential are impaired in their ability to fuse [163,164]. In contrast, mitochondrial fission appears to be a non-selective process that does not rely on

the membrane potential. Mitochondrial fission subsequently may act to protect the cell from the deleterious effects of mitochondrial damage, with segregation of unhealthy mitochondria from the network, and subsequent elimination by the specific autophagic process termed "mitophagy" [10,165]. Down regulation of Fis1 or expression of a Drp1 dominant negative mutant (Drp1$^{K38A}$) reduces mitophagy [10], suggesting that fission is a prerequisite for this process. In support of this, elongation of mitochondria during starvation has been shown to protect mitochondria from autophagic elimination [166,167]. This elongation occurs due to protein kinase A (PKA) dependent phosphorylation of Drp1 that inhibits fission [166,167]. However, knockout of Drp1 does not affect the efficiency of autophagy [42], suggesting that Drp1 is dispensable for this process in mammals. In addition, mitophagy in yeast has been shown to be independent of mitochondrial fission factors Dnm1, Fis1, Mdv1 and Caf4 [168], indicating that this process is regulated by a separate machinery.

The E3 ligase Parkin and the mitochondrial Pten induced kinase 1 (PINK1) have also been shown to be important in clearance of damaged mitochondria by mitophagy. Accumulation of PINK1 on mitochondria recruits Parkin to mitochondria upon mitochondrial depolarisation, resulting in ubiquitination and subsequent degradation of mitochondrial proteins including Mfn1/2 and Drp1 [105,117,169–173]. Mutations in the genes encoding these proteins have been identified in patients with Parkinson's disease [171,174–176]. Interestingly the mitochondrial phosphatase PGAM5 has been implicated in mitochondrial morphology through its reported interaction with PINK1, in addition to PGAM5 mediated Drp1 dephosphorylation [157,177]. Moreover, studies in *Drosophila* indicated that over-expression of PGAM5 leads to an increase in fission, whilst down-regulation causes an increase in mitochondrial elongation [177]. However, differences between *Drosophila* and mammalian mitochondrial morphology upon overexpression and down regulation of PINK1 have been reported previously [11,178–183], and further investigation of the potential role of PGAM5 in PINK1 mediated mitophagy in mammals is required.

## 8. Mitochondrial fission and disease

As mitochondria play a central role in cell metabolism, aberrant regulation of mitochondrial morphology is linked to a number of human diseases. For example, mutations in key mitochondrial morphology proteins are associated with certain pathologies. Mutations in the Mfn2 gene have been shown to cause the neurodegenerative disease Charcot-Marie-Tooth disease type 2A (CMT2A) [184]; mutations in OPA1 lead to a progressive blindness condition, autosomal dominant optic atrophy (ADOA) [185–187], mutation in GDAP1 causes Charcot-Marie-Tooth disease type 4A [92,188] and a dominant negative form of Drp1 results in a broad range of physiological abnormalities including optic atrophy and hypoplasia [44]. Changes in mitochondrial morphology can also manifest in a variety of other diseases, such as cardiomyopathy, diabetes and obesity [189–191]. In addition, the neurological disorders Alzheimer's and Parkinson's disease, are associated with mitochondrial dysfunction, and exhibit altered calcium homeostasis and elevated reactive oxygen species production [192–194].

Modifications altering Drp1 activity have been linked to human neurodegenerative pathologies, such as Alzheimer's, Parkinson's and Huntington's disease [101,105,194,195]. Mutant huntingtin triggers mitochondrial fragmentation by interaction with Drp1 in fibroblasts from patients with Huntington's disease [195,196]. This fragmentation could be rescued by reducing Drp1 GTPase activity with the dominant-negative Drp1 K38A mutant [195,196]. As mentioned previously, Parkinson's disease has been linked to the loss of PINK1 or Parkin function in human cells [171,174–176]. In mammalian PINK1 deficient cells, mitochondrial fragmentation is mediated by dephosphorylation of Drp1 by calcineurin [197]. However, it was recently reported that Drp1-independent fragmentation of mitochondria occurs by direct interaction of the protein α-synuclein with mitochondrial membranes [198], and point mutations in α-synuclein, have been described to cause an autosomal dominant form of Parkinson's disease [199–201]. Drp1 may well represent a new therapeutic target to combat neurodegeneration, however given the complex nature of these diseases and the multiple proteins identified that have a role in their pathogenesis, the central role of Drp1 has yet to be clarified.

## 9. Conclusion

Recent advances in the field of mitochondrial morphology have provided significant insights into the complex process of mitochondrial fission. Mitochondrial fission is an intricate process that is important for cellular division, neuronal synapse formation, and autophagy. Mitochondrial fission is essential in development and within specific cells and tissues but loss of fission does not prevent cytokinesis or cellular proliferation. In addition, in the absence of mitochondrial fission, apoptosis and autophagy can still proceed. Despite advances made in the understanding of mitochondrial dynamics a number of questions remain, including how the mitochondrial fission and fusion proteins are co-ordinated to maintain the reticular network, and the identification of the signalling pathways that regulate their activity. Whilst a number of new mediators of mitochondrial fission have been identified, how these proteins co-ordinate division of the double membrane is currently unknown. The reorganisation of mitochondrial proteins to form an active fission complex is likely to involve proteins that govern not only lipid modification, but also changes in membrane composition. Analysis of the lipid composition of mitochondrial membranes upon induction of fission or fusion may shed some light on the membrane remodelling events that are required to facilitate these processes. Communication and shared pathways between sub-cellular organelles are critical to correct cellular function. The role of proteins also varies within specific cells, with the energetic and metabolic requirements within varied cell types placing different demands on function. The reliance of neuronal cells on correct regulation of mitochondrial fission places this field at the forefront of investigations into neurodegeneration.

## Acknowledgements

This work was supported by grants from the Australian Research Council and the National Health and Medical Research Council of Australia.

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