Mitochondrial dynamics: overview of molecular mechanisms

Lisa Tilokani*, Shun Nagashima*, Vincent Paupe and Julien Prudent

Medical Research Council Mitochondrial Biology Unit, University of Cambridge, Wellcome Trust/MRC Building, Cambridge Biomedical Campus, Hills Road, Cambridge CB2 0XY, U.K.

Correspondence: Julien Prudent (julien.prudent@mrc-mbu.cam.ac.uk)

Mitochondria are highly dynamic organelles undergoing coordinated cycles of fission and fusion, referred as ‘mitochondrial dynamics’, in order to maintain their shape, distribution and size. Their transient and rapid morphological adaptations are crucial for many cellular processes such as cell cycle, immunity, apoptosis and mitochondrial quality control. Mutations in the core machinery components and defects in mitochondrial dynamics have been associated with numerous human diseases. These dynamic transitions are mainly ensured by large GTPases belonging to the Dynamin family. Mitochondrial fission is a multi-step process allowing the division of one mitochondrion in two daughter mitochondria. It is regulated by the recruitment of the GTPase Dynamin-related protein 1 (Drp1) by adaptors at actin- and endoplasmic reticulum-mediated mitochondrial constriction sites. Drp1 oligomerization followed by mitochondrial constriction leads to the recruitment of Dynamin 2 to terminate membrane scission. Inner mitochondrial membrane constriction has been proposed to be an independent process regulated by calcium influx. Mitochondrial fusion is driven by a two-step process with the outer mitochondrial membrane fusion mediated by mitofusins 1 and 2 followed by inner membrane fusion, mediated by optic atrophy 1. In addition to the role of membrane lipid composition, several members of the machinery can undergo post-translational modifications modulating these processes. Understanding the molecular mechanisms controlling mitochondrial dynamics is crucial to decipher how mitochondrial shape meets the function and to increase the knowledge on the molecular basis of diseases associated with morphology defects. This article will describe an overview of the molecular mechanisms that govern mitochondrial fission and fusion in mammals.

Introduction

For a long time, mitochondria have primarily been considered as the ‘powerhouse’ of the cell, producing the energy required for cell metabolism by oxidative phosphorylation (OXPHOS) [1,2]. It is now accepted that mitochondria are also involved in numerous other physiological processes such as programmed cell death, innate immunity, autophagy, redox signalling, calcium homeostasis and stem cells reprogramming [2-4]. Mitochondrial ultrastructure visualized by electron microscopy (EM) is characterized by a double membrane system. The outer mitochondrial membrane (OMM) faces the cytosol, and the inner mitochondrial membrane ( IMM ) protrudes into the mitochondrial matrix containing mitochondrial DNA (mtDNA). The compartment delimited by the IMM and the OMM is referred as the intermembrane space (IMS). However, the development of live cell imaging over the last 30 years has dramatically changed the concept of mitochondria being static and isolated structures. Indeed, mitochondria can modulate their morphology to create a tubular network coordinated by fission and fusion events. The balance between these two opposite processes regulates mitochondrial number, size and positioning within the cytoplasm and is referred as ‘mitochondrial dynamics’ [5].
Mitochondrial fission is characterized by the division of one mitochondrion into two daughter mitochondria, whereas mitochondrial fusion is the union of two mitochondria resulting in one mitochondrion. The deregulation of these spatio-temporal events results in either a fragmented network characterized by a large number of small round-shape mitochondria or a hyperfused network with elongated and highly connected mitochondria (Figure 1). These balanced dynamic transitions are not only required to ensure mitochondrial function but also to respond to cellular needs by adapting the network to nutrient availability and to the metabolic state of the cell [6]. Moreover, different morphological states are associated with multiple physiological and pathophysiological conditions [7]. Mitochondrial fragmentation is often linked to mitochondrial dysfunction as this morphological state predominates during elevated stress levels and cell death [8]. However, it is also observed in the phase G2/M of the cell cycle and is needed for mitochondrial motility, quality control and mtDNA inheritance [9,10]. Although still under debate, a fused mitochondrial network would allow matrix component distribution and stimulation of OXPHOS activity [11]. Mitochondrial elongation also confers protection against phagophore engulfment during autophagy triggered by nutrient starvation and is mainly associated with cell survival mechanisms [12].

The main proteins composing the core machinery are large GTPase proteins belonging to the Dynamin family (Figure 2). These mechanoenzymes can oligomerize and change conformation to drive membrane remodelling, constriction, scission and/or fusion [13]. Mitochondrial constriction and scission are carried out by the Dynamin-related-/like protein 1 (Drp1) and Dynamin2 (Dnm2), respectively [14]. Mitochondrial fusion is ensured by mitofusins 1 and 2 (Mfn1 and Mfn2) and optic atrophy 1 (OPA1), which mediate OMM and IMM fusion, respectively [15]. Knockout (KO) of either of these GTPases is embryonic lethal in mice and embryonic fibroblasts derived from these mice harbour dramatic mitochondrial morphology defects [16-19] (except for the Dnm2-KO mouse where mitochondrial morphology has not been investigated). The relevance of mitochondrial dynamics has also been highlighted in humans where pathogenic mutations in genes corresponding to the core fission machinery (Drp1 [20], Dnm2 [21], MFF [22] and Mid49 [23]), fusion (Mfn2 [24] and OPA1 [25,26]), and other factors involved in these events (e.g. MTO1 [27,28], GDAP1 [29] and SLC25A46 [30,31]) have been reported.

Together, this highlights the importance of understanding how mitochondrial morphology is regulated, in order to decipher how mitochondrial shape meets the function. In this article, we will present an overview of the recent proposed mechanisms regulating mitochondrial fission and fusion in mammals.

**Molecular mechanisms of mitochondrial fusion**

**Mitofusins and outer mitochondrial membrane fusion**

OMM fusion is ensured by the two large GTPases homologues Mfn1 and Mfn2 in mammals, which share approximately 80% sequence similarity in humans. The Mfn orthologue, fuzzy onion (Fzo1), was originally characterized in Drosophila melanogaster [32] and is conserved from yeast [33] to human [34]. Overexpression of either Mfn leads to mitochondrial aggregation around the nucleus [35]. While Mfn1-KO induces mitochondrial fragmentation, Mfn2-KO exhibits swollen spherical mitochondria [16]. This difference can be explained by the fact that Mfn1 has...
been shown to have a greater guanosine triphosphate (GTP)-dependent membrane tethering activity [36]. In addition, Mfn2 is not only involved in fusion but is also a key regulator of the mitochondria-endoplasmic reticulum (ER) contact sites tethering [37,38]. Nevertheless, overexpression of Mfn1 or Mfn2 in Mfn2-KO or Mfn1-KO MEF cells, respectively, can restore mitochondrial fusion [16]. Both proteins also accumulate at contact areas between two adjacent mitochondria [35] and establish homo or heterotypic complexes leading to mitochondrial fusion [39].

Globally, mitochondrial fusion is characterized by three different steps: the tethering of two mitochondria in trans, the docking of two membranes increasing the contact surface area and decreasing the distance between the two membranes [40], and finally the fusion of the two OMM due to conformational changes induced by GTP hydrolysis [36,41] (Figure 3).

Over the last 15 years, the proposed mechanism of mitochondrial fusion by mitofusins has been based on their topology. Like yeast Fzo1 [42], it was accepted that Mfn1 were inserted in the OMM via two transmembrane (TM) domains separated by a short loop exposing their N-terminal region containing the GTPase and the coil-coil heptad repeat 1 (HR1) domains and their C-terminal harbouring the HR2 domain in the cytosol [34,43-45] (Figures 2 and 3A). Based on this model and some structural insights, the required mechanistic steps of fusion have been proposed (Figure 3A).

For example, it has been proposed that Mfn1 dimeric antiparallel trans interactions between apposing mitochondria are established via their HR2 domains, followed by GTP hydrolysis resulting in OMM fusion [44].
Figure 3. Simplified models for mitochondrial fusion in mammals

(A) Schematic representations of mitochondrial fusion, based on the Mfns topology suggesting two TM domains with both the HR1 and HR2 domains facing the cytosol. (1) The outer membrane of two opposing mitochondria are tethered by the interaction in trans of the HR2 and/or GTPase domains of Mfns. GTP binding or/and hydrolysis induce Mfns conformational change leading to mitochondrial docking and to an increase of membrane contact sites. For clarity reasons, not all of the recent suggested models leading to Mfns dimerization and conformational change are highlighted in the scheme. (3) Finally, GTPase-dependent power stroke or GTP-dependent oligomerization ensure OMM fusion. The composition of the OMM in phospholipids can also regulate this process. (4) Following OMM fusion, OPA1 and CL drive IMM fusion. The interaction between OPA1 and CL on either side of the membrane tethers the two IMM, which fuse following OPA1-dependent GTP hydrolysis (5). In this model, S-OPA1 has been shown to enhance OPA1–CL interaction and fusion. Please note that after OMM and IMM fusion, Mfn2 and OPA1, as membrane-bound proteins, are still present on the different membranes but are disassembled. (B) Schematic representations of OMM fusion based on the new metazoan Mfns topology suggesting only one TM placing the Mfn C-terminus in the IMS. Oxidized environment in the IMS (ROS production) and increase concentration of GSSG lead to the establishment of two disulphide bonds within the IMS domain. These redox-mediated disulphide modifications induce the dimerization and oligomerization of Mfns molecules which may promote tethering or GTPase activity required for OMM fusion. Interestingly, this redox-regulated Mfns oligomerization is a dynamic and reversible process. Yellow stars indicate an oxidized environment.

In contrast to the HR2 trans model, more recent structural studies conducted with a ‘minimal’ recombinant Mfn1 (internal deletion of the HR2 and generation of the predicted TM domains) revealed that the tethering is mediating through the GTPase domains [46,47]. The fusion of the adjacent membranes may then be ensured by a GTPase-dependent power stroke [47] or GTP-dependent oligomerization [46]. While crystal structures clearly reveal
the GTPase binding in trans as a primary mechanism of tethering, a peptide that mimics the HR1 helix has also been shown to activate mitochondrial fusion [48]. These peptides, or smaller drugs that alter the conformation of HR1, increase mitochondrial fusion when added to cells. Based on modelling from the structures, the authors propose that these compounds interfere with HR1 binding to HR2, thereby opening the helix and promoting mitochondrial tethering and fusion [48]. These compounds were not tested in a direct mitochondrial fusion assay, so it remains possible that other mechanisms can explain their cellular effects. Finally, it has been recently proposed that the C-terminal tail of Mfn1, harbouring the HR2 domain, contains an amphipathic helix required for Mfn1 insertion and promoting mitochondrial fusion [49]. More recent work has shown that HR1, but not HR2, promotes liposome tethering and lipid mixing in reconstituted assays, hinting that this HR may destabilize the lipids to drive membrane fusion [50].

The idea that the Mfn form a larger fusion pore, visualized as a circular mitochondrial docking complex, has been suggested using cryo-electron microscopy in isolated yeast mitochondria [40]. This study has also revealed that the cycles of GTP hydrolysis are required to assemble this dynamic structure [40].

Importantly, the prediction that HR1 and HR2 both reside on the cytosolic side of the OMM was based on the established topology of the yeast orthologue Fzo1. However, this topology was recently challenged, forcing a reconsideration of the current models [51] (Figures 2 and 3B). Furthermore, phylogenetic analysis has revealed that MfnS from yeast and metazoans are highly divergent, with bioinformatics predicting a single TM domain in metazoan MfnS, with two membrane spanning regions in MfnS of the fungal clade. Classical biochemical experiments confirmed that human MfnS harbour only one TM domain, placing the ~12 kDa C-terminal and the HR2 domain in the IMS [51]. Interestingly, this new topology has been functionally linked to the control of mitochondrial fusion by redox signalling. Indeed, two cysteines located in the HR2 domains can be oxidized by increased level of oxidized glutathione leading to the formation of disulphide bonds between two MfnS molecules and their oligomerization required for membrane fusion [51]. These results confirmed initial studies describing the role of reactive oxygen species and oxidative stress in promoting mitochondrial fusion [52-54]. This new topology is consistent with the observation that HR2 did not drive liposome tethering or fusion [50]. Given the previous assumptions that the HR2 domain resides in the cytosol, this new topology raises a number of outstanding questions, for example: Are the GTPase domain interactions in trans sufficient to tether two mitochondrial fusions with HR1 domain driving bilayer mixing? Do the compounds interfering with HR1 domain affect additional Mfn partners that may participate in fusion?

Together, these data highlight the requirement of a reappraisal of the current acknowledged models and further experiments based on this new model should be performed in the near future to confirm and shed light on the full mechanism of OMM fusion.

**OPA1 and inner mitochondrial membrane fusion**

IMM fusion occurs downstream of OMM fusion and is mediated by the large GTPase OPA1 and specific IMM lipid components. Indeed, genetic loss of OPA1 leads to mitochondrial fragmentation whereas OPA1 overexpression induces mitochondrial elongation [55]. OPA1, originally described in the yeast model (Mgm1p) [56], is evolutionary conserved and is a complex protein with eight identified splice-variants. Its protein domain organization shares similarities with ‘classical’ dynamins (Figure 2). It is inserted within the IMM via a ~100 residues N-terminal matrix targeting signal followed by a TM domain, exposing the majority of the protein to the IMS [57]. Despite the role of the GTPase and GTPase effector domain (GED) domains for GTP hydrolysis, the specific roles of the different domains during fusion events are not well understood. OPA1 harbours at least two sites for proteolytic cleavage, which generate shorter and soluble fragments. These cleavages are mediated by two membrane-bound metalloproteases, OMA1 [58,59] and YME1L [60,61], cleaving the protein at S1 and S2 sites, respectively. This results in at least five OPA1 fragments detectable by immunoblot where the two higher molecular weight forms are referred as L-OPA1 and the three shorter as S-OPA1. The abundance of the different OPA1 isoforms is cellular context specific and affects mitochondrial dynamics regulation. Indeed, OMA1-dependent cleavage of OPA1 is a stress response, whereas stimulation of OXPHOS induces YME1L activity. It is interesting to note that a mild mitochondrial stress leads to a stress-induced mitochondrial hyperfusion (SIMH) mechanism regulated by the Stomatin-like protein 2, Mfn1 and OPA1 and acting as a pro-survival response [62].

Initial work has described the requirement of both L- and S-OPA1 isoforms to allow mitochondrial fusion since L-OPA1 and S-OPA1 alone have only little fusion activity [61]. However, recent studies have now shown that the L-OPA1 isoform alone is sufficient to drive fusion. Indeed, L-OPA1 accumulation drives fusion during SIMH [62] and is responsible for the mitochondrial hyperfusion observed in YME1L/OMA1-DKO cells [63]. The balance between OPA1 cleavage by OMA1 and YME1L plays a crucial role in fusion regulation and the precise role of the S-OPA1 generation is not perfectly understood [64]. Indeed, initial work has shown that S-OPA1 isoform is also able to induce
membrane tubulation in a liposome assay [65] and stimulation of OXPHOS induces YME1L-dependent S-OPA1 generation leading to mitochondrial fusion [66]. In contrast, mitochondrial stress-induced OPA1 cleavage by OMA1 can lead to mitochondrial fragmentation [58,59].

In mammals, OPA1 localization in only one of the two opposing mitochondria is sufficient to drive the fusion of both membranes [67]. These findings have been recently confirmed and a new model for IMM fusion regulated by OPA1 and a particular phospholipid has been proposed [68] (Figure 3A). As described later in this article, membrane lipid composition and in particular the lipid, cardioliopin (CL), play a crucial role in membrane remodelling and dynamics. CL is a mitochondria specific negatively charged lipid mainly localized in the IMM and required for the assembly and stability of large protein complexes like mitochondrial contact site and cristae organizing system (MICOS) and OXPHOS complexes [69]. Incubation of recombinant L-OPA1 with reconstituted CL-containing liposomes leads to a heterotypic interaction between L-OPA1 and CL driving membrane fusion [68]. In this model, S-OPA1 facilitates OPA1-CL binding and membranes fusion, corroborating studies performed in yeast showing the requirement of both S- and L-OPA1 isoforms as well as cardioliopin for IMM fusion [70,71]. Interestingly, these data have been validated in cellulo using a cell fusion assay, and suggest that the presence of OPA1 and CL on either side of the membrane can promote fusion and represents the minimal IMM fusion machinery [68]. These results also suggest that the OPA1 homotypic interaction is not involved in IMM fusion but in cristae architecture control.

Finally, OPA1-dependent IMM fusion depends on Mfn1 but not Mfn2 [62,72]. This observation raises the possible communication between the two membranes during fusion and suggests a potential interaction of Mfn1 with OPA1, a hypothesis now more plausible based on the new Mfns topology [51].

Overall, because of the complex processing of OPA1 and the lack of 3D structure of the protein, the precise mode of action of OPA1 has remained elusive. Further studies are needed to fully establish the mechanism of IMM fusion.

Molecular mechanisms of mitochondrial fission
Drp1 and adaptors
Mitochondrial fission is a multi-step process where the recruitment of the large GTPase Drp1 plays a crucial role. Drp1 is evolutionary conserved and its role in mitochondrial division was initially described in Caenorhabditis elegans [73] and yeast [74,75] before being extensively studied in mammals [76]. It is mainly a cytosolic protein, which is dynamically recruited to mitochondrial and peroxisomal membranes where it oligomerizes and drives membrane constriction in a GTP-dependent manner [14]. Indeed, genetic loss of Drp1 leads to a drastic elongation of both mitochondria and peroxisomes [77] in multiple cell lines and a variety of animal models [18,19].

Drp1 is composed of four distinct domains, an N-terminal GTPase domain followed by the middle domain, variable domain (or B-insert) and the GED in C-terminal (Figure 2). Like ‘classical dynamin’, Drp1 also contains bundle signalling elements (BSE) and stalk regions, but does not harbour the pleckstrin homology (PH) domain or the proline and arginine rich domain (PRD) at the C-terminal. The BSEs connect the GTPase domain with the stalk domain allowing Drp1 binding to membranes and subsequently its oligomerization [78].

During mitochondrial division, Drp1 is recruited to the OMM where it forms a ring-like structure around mitochondria leading to the narrowing of the membrane [76,78,79] (Figure 4). Then, GTP hydrolysis enhances this membrane constriction [80] which marks a potential future site of mitochondrial scission. Assembly of Drp1 at the OMM is mediated by the central stalk (middle domain) forming Drp1-oligomeric helices starting at two different points of the membrane [78,81]. Interestingly, in contrast with the common pathway where cytosolic Drp1 is directly recruited to a constriction site through its membrane-anchored adaptors, a ‘targeted equilibrium’ has been proposed. In this model, dimeric and oligomeric forms of Drp1 are in constant balance between the cytosol and mitochondria [82]. Mitochondria-bound Drp1 puncta can merge into a mature-sized Drp1 complex capable of moving laterally along the mitochondrial tubule, induce constriction and eventually fission [82].

As Drp1 lacks a PH domain to bind membrane phospholipids directly, its recruitment at the OMM requires adaptors proteins. In the yeast model, Dnm1 (Drp1 orthologue) is recruited to the OMM via the membrane-anchored protein fis1 [83] and two receptors Mdv1 [84] and Cae4 [85]. However, there are no obvious orthologues for Mdv1 and Cae4 in mammals and recent studies suggest that Fis1 is not involved in the fission mechanism in basal conditions [86]. Instead, the tail-anchored proteins mitochondrial fission factor (MFF) [87] and mitochondrial dynamics proteins 49 and 51 (MdD49 and MdD51) [88,89] act as receptors for Drp1 in mammals (Figures 2 and 4). On one hand, overexpression of MFF leads to a fragmented network [90] whereas MFF genetic invalidation induces mitochondrial and peroxisome elongation [87,90], accompanied by a decrease in Drp1 mitochondrial recruitment. Indeed, MFF can specifically recruit high-oligomeric forms of Drp1 in cellulo [91] and stimulate its GTPase [92] activity.
Figure 4. Simplified model for mitochondrial fission in mammals

Schematic representation of the multi-step processes required for mitochondria division. (1) In the matrix, replication of the mtDNA marks the site for ER-recruitment. In parallel, Drp1 oligomers are in constant balance between the cytosol and mitochondria. In addition, IMM constriction occurs at mitochondria–ER contacts in a Ca^{2+}-dependent process, before Drp1 oligomerization and maturation. (2) Oligomeric forms of Drp1 accumulate at ER-sites where the pre-constriction of the membrane has been initiated. (3) The zoomed area highlights the factors regulating mitochondrial division. The ER-bound INF2 and mitochondrial Spire1C induce actin nucleation and polymerization at mitochondria–ER contact sites. The Myosin IIA may ensure actin cable contraction, providing the mechanical force to drive mitochondria pre-constriction. At these sites, MFF and MiDs recruit Drp1 where it oligomerizes in a ring-like structure and (4) GTP-hydrolysis leads to conformational change, enhancing pre-existing mitochondrial constriction. The composition of the OMM in phospholipids also regulates Drp1 assembly and activity. (5) Then, Dnm2 is recruited to Drp1-mediated mitochondrial constriction neck where it assembles and terminates membrane scission, (6) leading to two daughter mitochondria. (7) The mechanisms of disassembly of the fission machinery following division remain unclear but both adaptors and Drp1 are found at both mitochondrial tips after division.
enhancing membrane constriction in liposome assay. On the other hand, MiDs overexpression leads to mitochondrial elongation due to Drp1 sequestration [88,93], whereas low levels induce mitochondrial fragmentation [94]. MiD49/51-DKO phenocopies MFF-KO, characterized by mitochondrial hyperfusion and Drp1 recruitment defects, showing a potential redundancy between MiD49 and MiD51 [86,95]. MiDs harbour a nucleotidyltransferase domain and MiD51 requires ADP as a cofactor to stimulate Drp1 oligomerization and GTPase activity [96,97]. However, in vitro experiments using MiD51-bound liposomes demonstrated the capacity of MiD51 to inhibit Drp1 GTPase activity [95]. While these receptors colocalize together in discrete foci with Drp1 at ER-constriction sites [86,94], MFF and MiD49/51 can act independently on Drp1 recruitment and activity [98]. Therefore, it is assumed that MFF and MiDs have distinct but complementary roles in mitochondrial fission where MiDs recruit GTP-bound state of Drp1 to facilitate oligomerization whereas MFF selectively recruits oligomeric and active forms of Drp1. These functional differences have been highlighted recently during the cell death programme [86]. Further work would shed light on the precise mechanisms of Drp1 recruitment by these adaptors.

**Final step of mitochondrial scission**

Although the role Drp1 plays in membrane constriction is well described, its capacity to terminate fission has always been questioned. Recombinant Drp1 expression leads to liposome tubulation but not to their scission [99]. Moreover, cryo-EM imaging in yeast showed that the most representative diameter of Dnm1-lipid tubes constriction upon addition of GTP was 50–60 nm [100], which suggested that final scission required an additional process. Recently, the canonical protein Dnm2, initially involved in endocytic vesicle scission, has been proposed to catalyse this final step [101] (Figure 4). Like Drp1, Dnm2 is a GTPase that assembles in a collar–like structure around the constricting lipid ‘necks’ of budding membrane–bound vesicles [13]. Live-cell imaging experiments have shown that Dnm2 acts downstream of mitochondrial Drp1 activity, is transiently and specifically recruited to ER- and Drp1-induced constriction sites and leads to fission [101]. In addition, silencing Dnm2 induces mitochondrial elongation and the presence of highly narrow and elongated super-constriction sites. This phenotype was not rescued by re-expression of Dnm2 mutants lacking its GTPase, PH or PRD domains suggesting that activity, lipid binding and localization of Dnm2 are required for its role in mitochondrial division [101].

**Mitochondrial division occurs at ER contact sites**

A groundbreaking discovery in the mitochondrial dynamics field was the discovery that the ER was required for the initial step of mitochondrial division. Indeed, high-resolution and 3D reconstructed images acquired using EM and tomography have shown that not only ER tubules make contact with mitochondria but they can also wrap around them leading to mitochondrial constriction [102] (Figure 4). This pre-constriction step is required to decrease the average mitochondrial diameter from approximately 300–500 nm to approximately 150 nm [102], to allow Drp1-oligomeric ring formation. Therefore, Drp1 and its adaptors MFF and MiD49/51 are also specifically recruited to these mitochondria–ER contact sites prior to mitochondrial division [95,102,103]. With recent evidence implicating the role of phospholipids [104] and calcium transfer [105,106] during the process, it is tempting to suggest that these ER contact sites are not just required for mitochondrial pre-constriction but also represent a signalling platform for metabolite exchange, facilitating membrane remodelling and division.

The ER-bound inverted-formin 2 (INF2) and the mitochondrial anchored formin-binding Spire1C are both actin-nucleating proteins (Figure 4). Silencing either protein leads to mitochondrial elongation and defects in actin polymerization at the mitochondria–ER interface [107,108]. At these contact sites, INF2 cooperates with Spire1C to regulate actin assembly required for mitochondrial constriction before Drp1 recruitment and oligomerization [107,108]. In addition, Myosin IIA may ensure actin cable contraction providing the mechanical force for pre-constriction site formation [109]. Furthermore, transient F-actin bursts have been observed at mitochondria just before Drp1-dependent mitochondrial division [110,111] and other proteins involved in actin cytoskeleton regulation have been shown to regulate mitochondrial fission such as coflin [110,112], cortactin [110], Arp2/3 [110] and Septin 2 [113]. Finally, Drp1 can bind F-actin in vitro which stimulates its oligomerization and its GTPase activity [114]. Together, the concomitant action of the ER and actin has clearly been identified as a crucial regulator of mitochondrial division and further studies will shed light on new potential regulators and their links with other members of the fission machinery.

Since the discovery of the role of the ER in mitochondrial division and the capacity of the oligomeric form of Drp1 to move along the tubules, it was unclear how the ER identifies and marks the sites for mitochondrial division. It had already been described that mitochondrial nucleoids were localized at mitochondria–ER contact sites in yeast [115] and mammal cells [116]. Recently, using high-resolution microscopy and live cell imaging, replicating mtDNA has
specifically been spatially associated at mitochondria–ER contacts and constrictions, marking future mitochondrial fission sites [117] (Figure 4), allowing mtDNA distribution to the two newly generated mitochondria. This new observation describes mtDNA replication as one of the first steps of mitochondrial division raising new questions about the regulating mechanism and how this signal coming from the matrix is transmitted to the ER.

**Constriction and division of the inner mitochondrial membrane**

While the mechanisms regulating OMM constriction are well documented, the events leading to IMM constriction or division are poorly understood. Until now, no machinery has been associated with IMM division. EM analyses in *C. elegans* [73] and from rat cardiomyocytes [118] reported the potential presence of IMM constriction or division in the absence of either Drp1 or OMM constriction, which suggested that it could happen early during the mitochondrial division process. However, only very recently, an underlying mechanism for IMM constriction and possibly division has been proposed.

Coupling EM to super-resolution microscopy, two recent studies have suggested that IMM constriction is Ca\(^{2+}\)-dependent and occurs at mitochondria–ER contact sites [105,106]. Stimulation of ER-induced calcium release to mitochondria leads to the constriction of the inner membrane compartment and may induce IMM division before Drp1 recruitment, therefore independently of OMM constriction [105,106]. In addition, this phenomenon is inhibited by the loss of the mitochondrial calcium uniporter (MCU), which also leads to mitochondrial elongation. This is consistent with previous work suggesting a link between mitochondrial Ca\(^{2+}\) influx and mitochondrial fragmentation [119]. While in human Osteosarcoma cells (U2OS), IMM constriction has been attributed to the stimulation of mitochondria–ER contacts and mitochondrial calcium uptake by INF2-mediated actin polymerization [105], in neurons this mechanism is ensured by OPA1 processing [106]. Indeed, calcium entry in mitochondria induces a drop in mitochondrial membrane potential leading to the activation of OMA1 and the processing of OPA1 in S-OPA1. S-OPA1 accumulation disrupts the capacity of the MICOS complex to stabilize OMM–IMM tethering, leading to the IMM untethering and possibly constriction [106]. This proposed mode of action confirms the role previously described for S-OPA1 in fission. Indeed, S-OPA1 can localize at mitochondria–ER contact sites with the OMM fission machinery, but also overexpression enhances mitochondrial fission [120]. However, further studies need to be performed to decipher the players regulating IMM constriction and division and precisely incorporate these events in the global mitochondrial division process.

**Additional layers of mitochondrial dynamics regulation**

**Membrane lipids composition in mitochondrial dynamics**

Phospholipids are the major components of mitochondrial membranes and their role in membrane curvature, remodelling and regulation of mitochondrial dynamics has recently emerged. Mitochondrial membranes are mainly composed of phosphatidylcholine and phosphoethanolamine but also contain minor amounts of other phospholipids like phosphatidic acid (PA) and cardiolipin (CL), which play a major role in membrane remodelling. PA, a saturated lipid, is directly transferred from the ER to mitochondria, where it is converted into CL at the IMM [121]. A small amount of CL can be located to the OMM where CL can be converted into PA by the OMM C-anchored member of the phospholipase D family, mitoPLD [104].

Initial work has demonstrated that overexpression of mitoPLD triggered mitochondrial hyperfusion, whereas its ablation inhibited fusion and induced mitochondrial fragmentation [122]. Interestingly, hydrolysis of OMM-localized PA in diacylglycerol (DAG) or lysoPA by cytosolic mitochondrial recruited PA phosphatase (lepin 1b) [123] or phospholipase (PA-PLA1) [124], respectively, inhibits fusion induced by PA accumulation. While PA accumulation enhances Mfn1/2-dependent OMM fusion [122], CL stimulates OPA1 assembly and GTPase activity, subsequently leading to liposomes membrane tubulation [65]. As described earlier, CL plays a major role in the heterotypic interaction with OPA1, which stimulates fusion and represents the minimum machinery to drive inner membranes fusion [68].

Although Drp1 lacks a specific PH domain, it has been shown that it can interact with both CL and PA. Drp1 binding to CL via its B-insert domain drives oligomerization and stimulation of its GTPase activity enhancing constriction and tubulation of liposome membranes [92,125–129], designating CL at the OMM as a pro-fission phospholipid. Interestingly, Drp1 oligomerization and GTP hydrolysis can rearrange liposome membranes containing CL to create a constricted membrane region enriched in CL and favourable to scission [126]. In contrast, PA synthesis by the mitoPLD negatively regulates Drp1-dependent mitochondrial division [130]. *In cellulo*, Drp1 binds directly PA, via an unstructured loop in its stalk domain, at the OMM constriction sites leading to its oligomerization but to an inhibition of its GTPase activity, which results in mitochondrial hyperfusion [130,131]. Overall, these studies highlight the antagonistic roles of PA and CL microdomain formation in mitochondrial fission and fusion regulation.
Post-translational modifications of the core components

Post-translational modifications of the core protein machinery have been extensively studied in the last 10 years (Figure 2). Drp1 phosphorylation has been the most studied and phosphorylation at serine 616 and serine 637 are considered as pro-fission and pro-fusion forms, respectively. During mitosis, Drp1 is phosphorylated by cdk1/cyclin B kinase dependent on serine 616, stimulating its oligomerization, subsequently inducing mitochondrial fission and ensuring organelle distribution to daughter cells [132]. Drp1 can also be phosphorylated by other kinases at this residue during cell death by protein kinase C (PKC) [133] and the Ca²⁺/calmodulin-dependent kinase II (CaMKII) [134,135] and by ERK-1/2 during cancer cell invasion [136,137] and cell reprogramming [138]. On the other hand, protein kinase A, recruited to mitochondria through A kinase-anchoring protein 1 (AKAP1), phosphorylates Drp1 on residue 637 inhibiting fission and protecting mitochondria from autophagosomal degradation during nutrient deprivation [139] and cell death [140,141]. Dephosphorylation of this residue is carried out by the calcium-dependent phosphatase calcineurin during cell death [140,142,143] and PGAM5 during necrosis [144]. Finally, other kinases including Rho-associated coiled-coil-containing protein kinase 1 (ROCK1) [145] and glycogen synthase kinase 3β (GSK3β) [146,147] can phosphorylate Drp1 and modulate mitochondrial morphology. In addition to phosphorylation, Drp1 can be dynamically SUMOylated/deSUMOylated on multiple non-consensus sites within the B domain controlling its stable association with the membrane, fission activity and cell death [148-153]. Drp1 can also be ubiquitinated by the RING-finger ubiquitin E3 ligase MARCH5/MITOL [154] and Parkin [155]. Finally, Drp1 activity can be controlled by S-nitrosylation [156-158] (but this regulation is still controversial) and O-GluNAcylation [159] modifications in its variable domain.

In addition, Drp1 receptors can also be regulated by post-translational modifications. Indeed, MFF is a substrate of the cellular energy sensor AMP-activated protein kinase (AMPK) upon mitochondrial dysfunction and a decrease in the cytosolic ATP/AMP ratio [160]. Phosphorylation of MFF enhances Drp1 recruitment, mitochondrial fission and damaged mitochondrial degradation [160]. Finally, MiD49 is also ubiquitinated by MARCH5/MITOL leading to its proteasomal degradation [161].

Post-translational modifications of mitochondrial fusion proteins are less documented. Indeed, the IMM OPA1 protein is regulated by proteolytic cleavage as already described, and only few modifications have been associated with Mfn1/Mfn2. The activity and stability of Mfn1 is regulated by ubiquitination and acetylation. MARCH5 ubiquitinates acetylated Mfn1 promoting its proteasomal degradation during mitochondrial stress [162]. During starvation, the protein deacetylase HDAC6 binds to and deacetylates Mfn1 enhancing fusion [163]. Finally, the phosphorylation of Mfn1 in the HR1 domain by the extracellular-signal-regulated kinase (ERK) inhibits mitochondrial fusion and promotes apoptosis [164].

Mfn2 can also be ubiquitinated by the HECT-type E3 ubiquitin-ligase Huwel [165], the RING-between RING type E3 ubiquitin-ligase Parkin [166], and the canonical RING-finger ligase MARCH5 [167] to control its activity and stability. Indeed, PINK1-phosphorylated Mfn2 can be ubiquitinated by Parkin leading to mitophagy [166] and JNK-phosphorylated Mfn2 can be ubiquitinated by Huwel, which leads to its degradation, facilitating fragmentation and apoptosis [165].

Other proteins regulating mitochondrial dynamics

While most work has focused on the core GTPases that govern mitochondrial dynamics, additional factors have been identified that either directly or indirectly modify mitochondrial dynamics.

Ganglioside-induced differentiation associated protein 1 (GDAP1) and SLC25A46 are two proteins which can control mitochondrial fission. GDAP1 has been proposed to participate in fission upstream MFF and Drp1 [29]. SLC25A46 has been suggested to be the mammalian orthologue of the yeast Ugo1, a protein interacting with Fzo1 and Mgm1 to coordinate outer and inner membrane fusion processes in yeast [168,169]. However, loss of SLC25A46 in human cells leads to mitochondrial hyperfusion probably due to a deregulation of mitochondrial membrane phospholipids composition suggesting that the role of SLC25A46 seems to have evolved toward a pro-fission function [30,31]. Finally, additional evidence suggests that inner mitochondrial compartments may drive mitochondrial division. An IMM protein, mitochondrial fission process 1 (MTPFP1), also called MTP18, has been involved in early step of mitochondrial division, upstream Drp1 activity [170,171]. Indeed, MTPFP1 loss induces mitochondrial hyperfusion and a deregulation of Drp1 phosphorylation in an unknown mechanism [172]. This small, inner membrane protein was recently shown to be a translational target of mTOR, where protein expression was lost upon starvation or inhibition of mTOR, driving mitochondrial hyperfusion which promoted cell survival [172].

MSTO1 (Misato) is a cytoplasmic regulator of the OMM fusion machinery since it depletion leads to impaired fusion [27,28]. Finally, the reactive oxygen species modulator 1 (ROMO1) protein has been identified as a
Mitochondrial dynamics: clinical syndromes

Pathogenic mutations in genes encoding the core fission and fusion machinery components have been linked to different severe human disorders, highlighting the physiological role of mitochondrial dynamics in cell homeostasis.

Table 1 Clinical syndromes due to mutations in genes encoding fission and fusion machinery components

| Gene   | OMIM    | Inheritance | Disease                                                                 | Symptoms                                                                                           | Refs |
|--------|---------|-------------|------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------|------|
| MFN2   | 608507  | AD          | Charcot–Marie–Tooth disease type 2A                                    | Distal limb muscle weakness and atrophy, axonal degeneration/regeneration, areflexia, distal sensory loss (pain and temperature more frequent) with or without: (a) CNS involvement (cognitive decline, spasticity, encephalopathy), (b) optic atrophy, (c) hearing loss and (d) vocal cord paresis | [24] [174] [178] |
|        |         | AR          | Charcot–Marie–Tooth disease type 2A                                    |                                                                                                     |      |
|        |         | AD          | Hereditary motor and sensory neuropathy V/A                             |                                                                                                     |      |
| OPA1   | 605290  | AD          | Optic atrophy 1                                                        | Progressive loss of visual acuity, temporal optic nerve pallor, central scotoma with or without: (a) CNS (ataxia, spasticity, hearing loss) and (b) PNS (axonal sensorineural polyneuropathy) symptoms. Early-onset optic atrophy accompanied by neurologic features, including ataxia, pyramidal signs, spasticity and mental retardation | [26] [26] |
|        |         | AD          | Optic atrophy plus syndrome                                             |                                                                                                     |      |
|        |         | AR          | Behr syndrome                                                          |                                                                                                     |      |
| MSTO1  | 617619  | AR/AD       | Myopathy and ataxia                                                    | Hand and feet muscle weakness, growth impairment, fine tremor, cerebellar hypotrophy with or without: (a) white matter hyperintensities, (b) frontal lobe atrophy and (c) mental retardation | [27] [28] |
| DNM1L  | 603850  | AR/AD       | Encephalopathy                                                         | Abnormal brain development, seizures, hepatic dysfunction, encephalopathy, dysmorphism.              | [20] [187] |
|        |         | AR          | Optic atrophy 5                                                        | Progressive loss of visual acuity, optic nerve atrophy and central scotoma                          | [188] |
| MFF    | 614785  | AR          | Encephalopathy                                                         | Seizures, dysphagia, optic and peripheral neuropathy, developmental delay, microcephaly, cerebellar atrophy and basal ganglia lesions | [22] |
| MEF2   | 615498  | AR          | Mitochondrial myopathy                                                 | Progressive muscle weakness, intermittent muscle pain and exercise intolerance                      | [23] |
| DNM2   | 602378  | AD          | Centronuclear myopathy 1                                               | Slowly progressive muscle weakness.                                                                | [21] |
|        |         | AD          | Charcot–Marie–Tooth disease, axonal type 2M                            | Distal limb muscle weakness and atrophy and sensory impairment, areflexia +/- neutropenia.          | [180] |
|        |         | AD          | Charcot–Marie–Tooth disease, dominant intermediate B                   | Polyhydramnios, decreased foetal movements, intracranial bleeding, retinal haemorrhage, joint contractures and respiratory insufficiency |      |
|        |         | AR          | Lethal congenital contracture syndrome 5                               |                                                                                                     |      |
| SLC25A46| 610826  | AR          | Pontocerebellar hypoplasia type 1                                      | Early onset of optic atrophy, peripheral axonal sensorimotor neuropathy, ataxia, myoclonus, cerebellar atrophy, hypotonia with variable degree of severity, age at onset and association of symptoms | [189] |
|        |         | AR          | Hereditary sensory motor neuropathy                                     |                                                                                                     | [31] |
|        |         | AR          | Optic atrophy spectrum disorders                                       |                                                                                                     | [30] |
| GDAP1  | 606598  | AR          | Charcot–Marie–Tooth disease type 4A                                    | Distal limb muscle weakness and atrophy and sensory impairment, areflexia with or without: (a) axonal regeneration and (b) vocal cord paresis | [176] [179] |
|        |         | AR          | Charcot–Marie–Tooth disease type 2K                                    |                                                                                                     |      |
|        |         | AR          | Charcot–Marie–Tooth disease type A                                     |                                                                                                     |      |
|        |         | AR          | Charcot–Marie–Tooth disease with vocal cord paresis                   |                                                                                                     |      |
| INF2   | 610982  | AD          | Charcot–Marie–Tooth disease type E                                     | Distal limb muscle weakness and atrophy and sensory impairment, areflexia, sensorineural hearing loss and foot drop | [177] |
|        |         | AD          | Focal segmental glomerulosclerosis                                     | Proteinuria and renal failure                                                                     | [179] |

A non-exhaustive list of the diseases related to the principal identified mutations in genes encoding the core components of mitochondrial dynamics with associated symptoms. Abbreviations: AD, autosomal dominant; AR, autosomal recessive; CNS, central nervous system; OMIM, Online Mendelian Inheritance in Man®; PNS, peripheral nervous system.
Mitochondria are highly dynamic organelles that remodel their network in order to maintain their shape, distribution and size.

The balance between fission and fusion events modulates mitochondrial morphology depending on the metabolic needs of the cell.

The components of the core machinery regulating mitochondrial dynamics belong to the Dynamin family and these mechano-GTPases enzymes ensure these dynamic transitions.

Mitochondrial dynamics are controlled by additional layers of regulation including the ER-actin axis, membranes lipid composition and post-translational modifications of the key proteins.

Conclusions
Mitochondrial fusion and fission are crucial events and it is evident that these dynamic morphological transitions control cell fate decisions. Elucidating how these events are regulated, from a molecular but also biological point of view, represents a crucial step to the understanding of numerous human diseases. The discovery of new players which regulate these events is in constant evolution, from unexpected organelles [190] to key biological events [191], and that will continue in the following years with the development of novel microscopy technology and genetic tools.
Mitochondrial fission and fusion regulate numerous physiological functions and numerous diseases have reported abnormal mitochondrial morphology.

Acknowledgments
We thank Dr Caterina Garone for constructive and helpful remarks on the mitochondrial dynamics and clinical syndromes section.

Funding
This work was supported by the Medical Research Council, UK (MC_UU_00015/7). L.T. is an MRC-funded PhD student. S.N. is a recipient of a Daiichi Sankyo Foundation of Life Science postdoctoral fellowship, Japan. V.P. is supported by a Marie Sklodowska-Curie postdoctoral fellowship.

Competing Interests
The authors declare that there are no competing interests associated with the manuscript.

Abbreviations
ADP, adenosine diphosphate; AMPK, AMP-dependent protein kinase; BDLP, bacterial dynamin-like protein; CaMKII, Ca2+/calmodulin-dependent kinase II; CL, cardiolipin; Dnm2, Dynamin 2; Drp1, Dynamin-related protein 1; ER, endoplasmic reticulum; GADAP1, ganglioside-induced differentiation associated protein 1; GTP, guanosine triphosphate; HR, heptad repeats; IMM, inner mitochondrial membrane; INF-2, inverted formin-2; MFF, mitochondrial fission factor; Mfn1, mitofusin 1; Mfn2, mitofusin 2; MID49, mitochondrial dynamic protein 49; MID51, mitochondrial dynamic protein 51; MSTO1, mitochondrial distribution and morphology regulator 1; mtDNA, mitochondrial DNA; MTFP1, mitochondrial fission process protein 1; OMA1, overlapping mitochondria; OPA1, optic atrophy protein 1; PA, phosphatidic acid; PH, pleckstrin homology; PKC, protein kinase C; PR, proline rich; ROMO, reactive oxygen species modulator; TM, transmembrane.

References
1 McBride, H.M., Neuspiel, M. and Wasiak, S. (2006) Mitochondria: more than just a powerhouse. Curr. Biol. 16, R551–R560, https://doi.org/10.1016/j.cub.2006.06.054
2 Kamer, K.J. and Moorthy, V.K. (2015) The molecular era of the mitochondrial calcium uniporter. Nat. Rev. Mol. Cell Biol. 16, 545–553, https://doi.org/10.1038/nrm4039
3 Nikoletopoulou, V., Markaki, M., Palikaras, K. and Tavernarakis, N. (2013) Crosstalk between apoptosis, necrosis and autophagy. Biochim. Biophys. Acta 1833, 3448–3459, https://doi.org/10.1016/j.bbamcr.2013.06.001
4 Rambold, A.S. and Pearce, E.L. (2018) Mitochondrial dynamics at the interface of immune cell metabolism and function. Trends Immunol. 39, 6–18, https://doi.org/10.1016/j.it.2017.08.006
5 Liesa, M., Palacin, M. and Zorzano, A. (2009) Mitochondrial dynamics in mammalian health and disease. Physiol. Rev. 89, 799–845, https://doi.org/10.1152/physrev.00030.2008
6 Wai, T. and Langer, T. (2016) Mitochondrial dynamics and metabolic regulation. Trends Endocrinol. Metab. 27, 105–117, https://doi.org/10.1016/j.tem.2015.12.001
7 Nunnari, J. and Suomalainen, A. (2012) Mitochondria: in sickness and in health. Cell 148, 1145–1159, https://doi.org/10.1016/j.cell.2012.02.035
8 Zemirli, N., Morel, E. and Molino, D. (2018) Mitochondrial dynamics in basal and stressful conditions. Int. J. Mol. Sci. 19, https://doi.org/10.3390/ijms19020564
9 Otera, H., Ishihara, N. and Miura, K. (2013) New insights into the function and regulation of mitochondrial fission. Biochim. Biophys. Acta 1833, 1256–1268, https://doi.org/10.1016/j.bbamcr.2013.02.002
10 Pickles, S., Vigie, P. and Youle, R.J. (2018) Mitophagy and quality control mechanisms in mitochondrial maintenance. Curr. Biol. 28, R170–R185, https://doi.org/10.1016/j.cub.2018.01.004
11 Mishra, P. and Chan, D.C. (2016) Metabolic regulation of mitochondrial dynamics. J. Cell Biol. 212, 379–387, https://doi.org/10.1083/jcb.201511036
12 Rambold, A.S., Kostelecky, B., Elia, N. and Lippincott-Schwartz, J. (2011) Tubular network formation protects mitochondria from autophagosomal degradation during nutrient starvation. Proc. Natl. Acad. Sci. U.S.A. 108, 10190–10195, https://doi.org/10.1073/pnas.1107402108
13 Ferguson, S.M. and De Camilli, P. (2012) Dynamin, a membrane-remodelling GTPase. Nat. Rev. Mol. Cell Biol. 13, 75–88, https://doi.org/10.1038/nrm3266
14 Kraus, F. and Ryan, M.T. (2017) The constriction and scission machineries involved in mitochondrial fission. J. Cell Sci. 130, 2953–2960, https://doi.org/10.1242/jcs.199562
15 Pernas, L. and Scorrono, L. (2016) Mito-morphosis: mitochondrial fusion, fission, and cristae remodeling as key mediators of cellular function. Annu. Rev. Physiol. 78, 505–531, https://doi.org/10.1146/annurev-physiol-021115-105011
16 Chen, H., Detmer, S.A., Ewald, A.J., Griffin, E.E., Fraser, S.E. and Chan, D.C. (2003) Mitofusins Mfn1 and Mfn2 coordinate regulate mitochondrial fusion and are essential for embryonic development. J. Cell Biol. 160, 189–200, https://doi.org/10.1083/jcb.200211046

© 2018 The Author(s). This is an open access article published by Portland Press Limited on behalf of the Biochemical Society and distributed under the Creative Commons Attribution License 4.0 (CC BY).
31. Hales, K.G. and Fuller, M.T. (1997) Developmentally regulated mitochondrial fusion mediated by a conserved, novel, predicted GTPase. Cell 90, 121–129, https://doi.org/10.1016/S0092-8674(00)80319-0
32. Hermann, G.J., Thatcher, J.W., Mills, J.P., Hales, K.G., Fuller, M.T., Nunnari, J. et al. (1998) Mitochondrial fusion in yeast requires the transmembrane GTPase Fzo1p. J. Cell Biol. 143, 359–373, https://doi.org/10.1083/jcb.143.2.359
33. Santel, A. and Fuller, M.T. (2001) Control of mitochondrial morphology by a human mitofusin. J. Cell Sci. 114, 867–874
34. Eura, Y., Ishihara, N., Yokota, S. and Mihara, K. (2003) Two mitofusin proteins, mammalian homologues of Fzo, with distinct functions are both required for mitochondrial fusion. J. Biochem. 133, 333–344, https://doi.org/10.1093/jb/mvg150
35. Ishihara, N., Eura, Y. and Mihara, K. (2004) Mitofusin 1 and 2 play distinct roles in mitochondrial fusion reactions via GTPase activity. J. Cell Sci. 117, 6535–6546, https://doi.org/10.1242/jcs.01565
36. de Brito, O.M. and Scorrano, L. (2008) Mitofusin 2 tethers endoplasmic reticulum to mitochondria. Nature 456, 605–610, https://doi.org/10.1038/nature07534
37. Filardi, P., Grooti, E., Turacchio, G., Luini, A., Pozzan, T. and Pizzo, P. (2015) Mitofusin 2 ablation increases endoplasmic reticulum-mitochondria coupling. Proc. Natl. Acad. Sci. U.S.A. 112, E2174–E2181, https://doi.org/10.1073/pnas.1504880112
38. Hoppins, S., Edlich, F., Cleland, M.M., Banerjee, S., McCaffrey, J.M., Youle, R.J. et al. (2011) The soluble form of Bax regulates mitochondrial fusion via Mfn2 homotypic complexes. Mol. Cell 41, 150–160, https://doi.org/10.1016/j.molcel.2010.11.030
39. Brandt, T., Cavellini, L., Kuhlbrandt, W. and Cohen, M.M. (2016) A mitofusin-dependent docking ring complex triggers mitochondrial fusion in vitro. Elife 5, e14618, https://doi.org/10.7554/eLife.14618
40. Legros, F., Lombez, A., Frachon, P. and Rojo, M. (2002) Mitochondrial fusion in human cells is efficient, requires the inner membrane potential, and is mediated by mitofusins. Mol. Biol. Cell 13, 4343–4354, https://doi.org/10.1091/mbc.e02-06-0330
41. Low, H.H., Sachse, C., Amos, L.A. and Lowe, J. (2009) Structure of a bacterial dynamin-like protein lipid tube provides a mechanism for assembly and membrane curving. Cell 139, 1342–1352, https://doi.org/10.1016/j.cell.2009.11.003
42. Rojo, M., Legros, F., Chateau, D. and Lombez, A. (2002) Membrane topology and mitochondrial targeting of mitofusins, ubiquitous mammalian homologs of the transmembrane GTPase Fzo. J. Cell Sci. 115, 1663–1674
43. Koshiba, T., Detmer, S.A., Kaiser, J.T., Chen, H., McCaffrey, J.M. and Chan, D.C. (2004) Structural basis of mitochondrial tethering by mitofusin complexes. Science 305, 858–862, https://doi.org/10.1126/science.1099793
44. Huang, P., Galloway, C.A. and Yoon, Y. (2011) Control of mitochondrial morphology through differential interactions of mitochondrial fusion and fission proteins. PLoS One 6, e20655, https://doi.org/10.1371/journal.pone.0020655
74 Bleazard, W., McCaffery, J.M., King, E.J., Bale, A.M., Zappaterra, M.D., Rube, D.A. and van der Bliek, A.M. (1999) C. elegans dynamin-related protein DRP-1 controls severing of the mitochondrial membrane. Mol. Biol. Cell 10, 2342–2356, https://doi.org/10.1091/mbc.09-12-0788

75 Olichon, A., Emorine, L.J., Descoines, E., Pelloquin, L., Brihese, L., Gas, N. et al. (2002) The human dynamin-related protein OPAL is anchored to the mitochondrial inner membrane facing the inter-membrane space. FEBS Lett. 523, 171–176, https://doi.org/10.1016/S0014-5793(02)09885-X

76 Head, B., Grapic, L., Amiri, M., Gandre-Babbe, S. and van der Bliek, A.M. (2009) Inducible proteolytic inactivation of OPAL mediated by the OMA1 protease in mammalian cells. J. Cell Biol. 182, 959–966, https://doi.org/10.1083/jcb.200906083

77 Ehres, S., Raschke, I., Mancuso, G., Bernacchia, A., Geimer, S., Tondora, B. et al. (2009) Regulation of OPAL processing and mitochondrial fusion by m-AAA protease isoenzymes and OMA1. J. Cell Biol. 187, 1023–1036, https://doi.org/10.1083/jcb.200906084

78 Grapic, L., Kanazawa, T. and van der Bliek, A.M. (2007) Regulation of the mitochondrial dynamin-like protein OPAL by proteolytic cleavage. J. Cell Biol. 178, 757–764, https://doi.org/10.1083/jcb.200704110

79 Song, Z., Chen, H., Fiket, M., Alexander, C. and Chan, D.C. (2007) OPAL processing controls mitochondrial fusion and is regulated by mRNA splicing, membrane potential, and Yme1L. J. Cell Biol. 178, 749–755, https://doi.org/10.1083/jcb.200704110

80 Tondora, D., Grandemange, S., Jourdain, A., Karbowski, M., Mattenberger, Y., Herzig, S. et al. (2009) SLP-2 is required for stress-induced mitochondrial hyperfusion. EMBO J. 28, 1589–1600, https://doi.org/10.1038/emboj.2009.89

81 Anand, R., Wall, T., Baker, M.J., Kladt, N., Schau, C.A., Ruggiar, E. et al. (2014) The m-AAA protease YME1L and OMA1 cleave OPAL to balance mitochondrial fusion and fission. J. Cell Biol. 204, 919–929, https://doi.org/10.1083/jcb.201308006

82 MacVicar, T. and Langer, T. (2016) OPAL processing in cell death and disease - the long and short of it. J. Cell Sci. 129, 2297–2306, https://doi.org/10.1242/jcs.159186

83 Bann, T., Heymann, J.A., Song, Z., Hinshaw, J.E. and Chan, D.C. (2010) OPAL disease alleles causing dominant optic atrophy have defects in cardiolipin-stimulated GFP hydrolysis and membrane tubulation. Hum. Mol. Genet. 19, 2113–2122, https://doi.org/10.1093/hmg/ddq686

84 Mishra, P., Carelli, V., Manfredi, G. and Chan, D.C. (2014) Proteolytic cleavage of OPAL stimulates mitochondrial inner membrane fusion and couples fusion to oxidative phosphorylation. Cell Metab. 19, 630–641, https://doi.org/10.1016/j.cmet.2014.03.011

85 Song, Z., Ghochani, M., McCaffrey, J.M., Frey, T.G. and Chan, D.C. (2009) Mitofusins and OPAL mediate sequential steps in mitochondrial membrane fusion. Mol. Biol. Cell 20, 3525–3532, https://doi.org/10.1091/mbc.e09-03-0252

86 Ban, T., Ishihara, T., Kohno, H., Saiia, I., Ichihara, A., Maenaka, K. et al. (2017) Molecular basis of selective mitochondrial fusion by heterotypic action between OPAL and cardiolipin. Nat. Cell Biol. 19, 856–863, https://doi.org/10.1038/ncc3560

87 Cogliati, S., Enriquez, J.A. and Scorrano, L. (2016) Mitochondrial Cristae: Where Beauty Meets Functionality. Trends Biochem. Sci. 41, 261–273, https://doi.org/10.1016/j.tibs.2016.01.001

88 DeVay, R.M., Dominguez-Ramirez, L., Lackner, L.L., Hoppins, S., Stahlberg, H. and Nunnari, J. (2009) Coassembly of Mgm1 isomorphs requires cardiolipin and mediates mitochondrial inner membrane fusion. J. Cell Biol. 186, 793–803, https://doi.org/10.1083/jcb.200906089

89 Ruijiviht, J., Megli, G., Rubinstein, J.L. and McQuilbin, G.A. (2009) Phospholipid association is essential for dynamin-related protein Mgm1 to function in mitochondrial membrane fusion. J. Biol. Chem. 284, 28682–28686, https://doi.org/10.1074/jbc.M109.049433

90 Cipiolat, S., Martins de Brito, O., Dal Zilio, B. and Scorrano, L. (2004) OPAL requires mitofusin 1 to promote mitochondrial fusion. Proc. Natl. Acad. Sci. U.S.A. 101, 15927–15932, https://doi.org/10.1073/pnas.1001979101

91 Labrousse, A.M., Zapata, M.D., Rube, D.A. and van der Bliiek, A.M. (1999) C. elegans dynamin-related protein DRP-1 controls severing of the mitochondrial outer membrane. Mol. Cell 4, 815–826, https://doi.org/10.1006/mccl.1999.30391-3

92 Bleazard, W., McCaffrey, J.M., King, E.J., Bale, S., Moczy, A., Tieu, Q. et al. (1999) The dynamin-related GTPase Dnm1 regulates mitochondrial fission in yeast. Nat. Cell Biol. 1, 298–304, https://doi.org/10.1038/13014

93 Sasaki, H. and Jensen, R.E. (1999) Division versus fusion: Dnm1p and Fzo1p antagonistically regulate mitochondrial shape. J. Cell Biol. 147, 699–706, https://doi.org/10.1083/jcb.147.4.699
105 Chakrabarti, R., Ji, W.K., Stan, R.V., de Juan Sanz, J., Ryan, T.A. and Higgs, H.N. (2018) INF2-mediated actin polymerization at the ER stimulates mitochondrial calcium uptake, inner membrane constriction, and division. J. Cell Biol. 217, 251–268, https://doi.org/10.1083/jcb.201709111

106 Cho, B., Cho, H.M., Jo, Y., Kim, H.D., Song, M., Moon, C. et al. (2017) Constriction of the mitochondrial inner compartment is a priming event for mitochondrial division. Nat. Commun. 8, 15754, https://doi.org/10.1038/ncomms15754

107 Manor, U., Bartholomew, S., Golani, G., Christenson, E., Kozlov, M., Higgs, H. et al. (2015) A mitochondria-anchored isoform of the actin-nucleating spire protein regulates mitochondrial division. Elite 4, e00828, https://doi.org/10.7554/elife.08828

108 Korobova, F., Ramabhadran, V. and Higgs, H.N. (2013) An actin-dependent step in mitochondrial fission mediated by the ER-associated formin INF2. Science 339, 464–467, https://doi.org/10.1126/science.1228360

109 Korobova, F., Gauvin, T.J. and Higgs, H.N. (2014) A role for myosin II in mammalian mitochondrial fission. Curr. Biol. 24, 409–414, https://doi.org/10.1016/j.cub.2013.12.032

110 Li, S., Xu, S., Roelofs, B.A., Boyman, L., Lederer, W.J., Sasaki, H. et al. (2015) Transient assembly of F-actin on the outer mitochondrial membrane contributes to mitochondrial fission. J. Cell Biol. 208, 109–123, https://doi.org/10.1083/jcb.201404050

111 Moore, A.S., Wong, Y.C., Simpson, C.L. and Holzbaur, E.L. (2016) Dynamic actin cycling through mitochondrial subpopulations locally regulates the fission-fusion balance within mitochondrial networks. Nat. Commun. 7, 12886, https://doi.org/10.1038/ncomms12886

112 Rehklau, K., Hoffmann, L., Gurniak, C.B., Ott, M., Witke, W., Scorrano, L. et al. (2017) Cofilin1-dependent actin dynamics control DRP1-mediated mitochondrial fission. Cell Death Dis. 8, e3063, https://doi.org/10.1038/cddis.2017.448

113 Pagliuso, A., Tham, T.N., Stevens, J.K., Lagache, T., Persson, R., Salles, A. et al. (2016) A role for septin 2 in Drp1-mediated mitochondrial fission. EMBO Rep. 17, 858–873, https://doi.org/10.15222/embr.201541612

114 Ji, W.K., Chakrabarti, R., Fan, X., Schoenfeld, L., Strack, S. and Higgs, H.N. (2017) Receptor-mediated Drp1 oligomerization on endoplasmic reticulum. J. Cell Biol. 216, 4123–4139, https://doi.org/10.1083/jcb.201610057

115 Murley, A., Lackner, L.L., Osman, C., West, M., Voeltz, G.K., Walter, P. et al. (2013) ER-associated mitochondrial division links the synthesis of mitochondria and mitochondrial DNA in yeast. Elite 2, e00422, https://doi.org/10.7554/eLife.00422

116 Ban-Ishihara, R., Ishihara, T., Sasaki, N., Mihara, K. and Ishihara, N. (2013) Dynamics of nucleoid structure regulated by mitochondrial fission contributes to cristae reformation and release of cytochrome c. Proc. Natl. Acad. Sci. U.S.A. 110, 11863–11868, https://doi.org/10.1073/pnas.1301951110

117 Lewis, S.C., Uchiyama, L.F. and Nunnari, J. (2016) ER-mitochondria contacts couple mtDNA synthesis with mitochondrial division in human cells. Science 353, aa5549, https://doi.org/10.1126/science.aaf5549

118 Fujikawa, H., Tandler, B. and Heppel, C.L. (2012) Mitochondrial division in rat cardiomyocytes: an electron microscope study. Anat. Rec. 295, 1455–1461, https://doi.org/10.1002/ar.22523

119 Hom, J.R., Gewandter, J.S., Michael, L., Sheu, S.S. and Yoon, Y. (2007) Thapsigargin induces biphasic fragmentation of mitochondria through calcium-mediated mitochondrial fission and apoptosis. J. Cell Physiol. 212, 498–508, https://doi.org/10.1002/jcp.21051

120 Baker, M.J., Tatsuta, T. and Langer, T. (2011) Quality control of mitochondrial proteostasis. Cold Spring Harb. Perspect. Biol. 3, a007559, https://doi.org/10.1101/cshperspect.a007559

121 Vance, J.E. (2015) Phospholipid synthesis and transport in mammalian cells. Traffic 16, 1–18, https://doi.org/10.1111/tra.12230

122 Choi, S.Y., Huang, P., Jenkins, G.M., Chan, D.C., Schiller, J. and Frohman, M.A. (2006) A common lipid links Mfn-mediated mitochondrial fusion and SNARE-regulated exocytosis. Nat. Cell Biol. 8, 1255–1262, https://doi.org/10.1038/ncb1487

123 Huang, H., Gao, Q., Peng, X., Choi, S.Y., Sarma, K., Ren, H. et al. (2011) piRNA-associated germine nuage formation and spermatogenesis require MitoPLD prosaposin mitochondrial-surface lipid signaling. Dev. Cell 20, 376–387, https://doi.org/10.1016/j.devcel.2011.01.004

124 Baba, T., Kashiwagi, Y., Arimitsu, N., Kogure, T., Edo, A., Maruyama, T. et al. (2014) Phospholipid acid (PA)-preferring phospholipase A1 regulates mitochondrial dynamics. J. Cell Biol. 209, 11497–11511, https://doi.org/10.1083/jcb.201313.31921

125 Bustillo-Zaballarreta, I., Montessuit, S., Raemy, E., Basanze, G., Terrones, O. and Martinou, J.C. (2014) Specific interaction with cardiolipin triggers functional activation of Dynamin-related protein 1. PLoS One 9, e102738, https://doi.org/10.1371/journal.pone.0102738

126 Stepanyants, N., Macdonald, P.J., Francy, C.A., Mears, J.A., Qi, X. and Ramachandran, R. (2015) Cardiolipin’s propensity for phase transition and its reorganization by dynamin-related protein 1 form a basis for mitochondrial membrane fission. Mol. Biol. Cell 26, 3104–3116, https://doi.org/10.1091/mbc.e15-06-0330

127 Macdonald, P.J., Stepanyants, N., Mehrótra, N., Mears, J.A., Qi, X., Sasaki, H. et al. (2014) A dimeric equilibrium intermediate nucleates Drp1 reassembly on mammalian membranes for fission. Mol. Biol. Cell 25, 1905–1915, https://doi.org/10.1091/mbc.e14-02-0728

128 Ugarte-Uribe, B., Muller, H.M., Otsuki, M., Nickel, W. and Garcia-Saez, A.J. (2014) Dynamin-related protein 1 (Drp1) promotes structural intermediates of membrane division. J. Biol. Chem. 289, 30645–30656, https://doi.org/10.1074/jbc.M114.577579

129 Francy, C.A., Alvarez, F.J., Zhou, L., Ramachandran, R. and Mears, J.A. (2015) The mechanoenzymatic core of dynamin-related protein 1 comprises the minimal machinery required for membrane constriction. J. Biol. Chem. 290, 11692–11703, https://doi.org/10.1074/jbc.M114.610881

130 Adachi, Y., Itoh, K., Yamada, T., Cerveny, K.L., Suzuki, T.L., Macdonald, P. et al. (2016) Coincident phosphatidic acid interaction restrains Drp1 in mitochondrial division. Mol. Cell 63, 1034–1043, https://doi.org/10.1016/j.molcel.2016.08.013

131 Adachi, Y., Iijima, M. and Sasaki, H. (2017) An unstructured loop that is critical for interactions of the stalk domain of Drp1 with saturated phosphatidic acid. Small GTPases 1–8, https://doi.org/10.1080/21541248.2017.1321614

132 Taguchi, N., Ishihara, N., Jofuku, A., Oka, T. and Mihara, K. (2007) Mitotic phosphorylation of dynamin-related GTPase Drp1 participates in mitochondrial fission. J. Biol. Chem. 282, 11521–11529, https://doi.org/10.1074/jbc.M607279200

133 Qi, X., Disatnik, M.H., Shen, N., Sobel, R.A. and Mochly-Rosen, D. (2011) Aberrant mitochondrial fission in neurons induced by protein kinase C (delta) under oxidative stress conditions in vivo. Mol. Biol. Cell 22, 256–265, https://doi.org/10.1091/mbc.e10-06-0551
134 Kim, D.I., Lee, K.H., Gabr, A.A., Choi, G.E., Kim, J.S., Ko, S.H. et al. (2016) Abeta-Induced Drp1 phosphorylation through Akt activation promotes excessive mitochondrial fission leading to neuronal apoptosis. Biochim. Biophys. Acta 1863, 2820–2834, https://doi.org/10.1016/j.bbamcr.2016.09.003

135 Xu, S., Wang, P., Zhang, H., Gong, G., Gutierrez Cortes, N., Zhu, W. et al. (2016) CaMKII induces permeability transition through Drp1 phosphorylation during chronic beta-AR stimulation. Nat. Commun. 7, 13189, https://doi.org/10.1038/ncomms13189

136 Serafimova, M.N., Wieder, S.Y., Renaut, T.T., Elkhori, R., Ascoli, J.J., Yao, J.L. et al. (2015) Mitochondrial division is requisite for RAS-induced transformation and targeted by oncogenic MAPK pathway inhibitors. Mol. Cell 57, 521–536, https://doi.org/10.1016/j.molcel.2015.01.003

137 Kashatus, J.A., Nascimento, A., Myers, L.J., Sher, A., Byrne, F.L., Hoehn, K.L. et al. (2015) Erk2 phosphorylation of Drp1 promotes mitochondrial fission and MAPK-driven tumor growth. Mol. Cell 57, 537–551, https://doi.org/10.1016/j.molcel.2015.01.002

138 Prieto, J., Leon, M., Ponsoda, X., Sendra, R., Bort, R., Ferrer-Lorente, R. et al. (2016) Early ERK1/2 activation promotes DRP1-dependent mitochondrial fission necessary for cell reprogramming. Nat. Commun. 7, 11124, https://doi.org/10.1038/ncomms11124

139 Gomes, L.C., Di Benedetto, G. and Scorrano, L. (2011) During autophagy mitochondria elongate, are spared from degradation and sustain cell viability. Nat. Cell Biol. 13, 589–598, https://doi.org/10.1038/ncb2220

140 Cribbs, J.T. and Strack, S. (2007) Reversible phosphorylation of Drp1 by cyclic AMP-dependent protein kinase and calcineurin regulates mitochondrial fission and cell death. EMBO Rep. 8, 939–944, https://doi.org/10.1038/sj.embor.7401062

141 Chang, C.R. and Blackstone, C. (2007) Cyclic AMP-dependent protein kinase phosphorylation of Drp1 regulates its GTPase activity and mitochondrial morphology. J. Biol. Chem. 282, 21583–21587, https://doi.org/10.1074/jbc.C700083200

142 Cereghetti, G.M., Stangerlin, A., Martín de Brito, O., Chang, C.R., Blackstone, C., Bernardi, P. et al. (2008) Diphosphorylation by calcineurin regulates translocation of Drp1 to mitochondria. Proc. Natl. Acad. Sci. U.S.A. 105, 15803–15808, https://doi.org/10.1073/pnas.0800249105

143 Slupe, A.M., Merrill, R.A., Flippo, K.H., Lobas, M.A., Houtman, J.C. and Strack, S. (2013) A calcineurin docking motif (LXVP) in dynamic-related protein 2 contributes to mitochondrial fragmentation and ischemic neuronal injury. J. Biol. Chem. 288, 12353–12365, https://doi.org/10.1074/jbc.M113.459677

144 Wang, Z., Jiang, H., Chen, S., Du, F. and Wang, X. (2012) The mitochondrial phosphatase PGAM5 functions at the convergence point of multiple necrotic death pathways. Cell 148, 226–243, https://doi.org/10.1016/j.cell.2011.11.030

145 Wang, W., Wang, Y., Long, J., Wang, J., Haudek, S.B., Overbeek, P. et al. (2012) Mitochondrial fission triggered by hyperglycemia is mediated by ROCK1 activation in podocytes and endothelial cells. Cell Metab. 15, 186–200, https://doi.org/10.1016/j.cmet.2012.01.009

146 Chou, C.H., Lin, C.C., Yang, M.C., Wei, C.C., Liao, H.D., Lin, R.C. et al. (2012) GSK3beta-mediated Drp1 phosphorylation induced elongated mitochondrial morphology against oxidative stress. PLoS One 7, e94112, https://doi.org/10.1371/journal.pone.0049112

147 Yan, J., Liu, X.H., Han, M.Z., Wang, Y.M., Sun, X.L., Yu, N. et al. (2015) Blockage of GSK3beta-mediated Drp1 phosphorylation provides neuroprotection in neuronal and mouse models of Alzheimer’s disease. Neurobiol. Aging 36, 211–227, https://doi.org/10.1016/j.neurobiolaging.2014.08.005

148 Braschi, E., Zunino, R. and McBride, H.M. (2009) MAPL is a new mitochondrial SUMO E3 ligase that regulates mitochondrial fission. EMBO Rep. 10, 748–754, https://doi.org/10.1038/sj.embr.7400986

149 Wasiak, S., Zunino, R. and McBride, H.M. (2007) Bax/Bak promote sumoylation of DRP1 and its stable association with mitochondria during apoptotic cell death. J. Biol. Chem. 282, 439–450, https://doi.org/10.1074/jbc.M6010042

150 Zunino, R., Braschi, E., Xu, L. and McBride, H.M. (2009) Translocation of SenP5 from the nucleoli to the mitochondria modulates DRP1-dependent fission during mitosis. J. Biol. Chem. 284, 17783–17795, https://doi.org/10.1074/jbc.M90192200

151 Prudent, J., Zunino, R., Sugiuara, A., Mattie, S., Shore, G.C. and McBride, H.M. (2015) MAPL SUMOylation of Drp1 stabilizes an ER/mitochondrial platform required for cell death. Mol. Cell 59, 941–955, https://doi.org/10.1016/j.molcel.2015.08.001

152 Fu, J., Yu, H.M., Chiu, S.Y., Miranda, A.J., Maruyama, E.O., Cheng, J.G. et al. (2014) Disruption of SUMO-specific protease 2 promotes oxidative stress-mediated neurodegeneration. Plos Genet. 10, e1004579, https://doi.org/10.1371/journal.pgen.1004579

153 Guo, C., Hildick, K.L., Luo, J., Dearden, L., Wilkinson, K.A. and Henley, J.M. (2013) SENP3-mediated deSUMOylation of dynamin-related protein 1 promotes cell death following ischaemia. EMBO J. 32, 1514–1528, https://doi.org/10.1038/emboj.2013.65

154 Karbowski, M., Neutzen, A. and Youle, R.J. (2007) The mitochondrial E3 ubiquitin ligase MARCH5 is required for Drp1 dependent mitochondrial division. J Cell Biol. 178, 71–84, https://doi.org/10.1083/jcb.200611064

155 Wang, H., Song, P., Du, L., Tian, W., Yue, W., Liu, M. et al. (2011) Parkin ubiquitinitates Drp1 for proteasome-dependent degradation: implication of dysregulated mitochondrial dynamics in Parkinson disease. J. Biol. Chem. 286, 11649–11658, https://doi.org/10.1074/jbc.M110.144238

156 Cho, D.H., Nakamura, T., Fang, J., Cleplak, P., Godzik, A., Gu, Z. et al. (2009) S-nitrosylation of Drp1 mediates beta-amyloid-related mitochondrial fission and neuronal injury. Science 324, 102–105, https://doi.org/10.1126/science.1171901

157 Bossy, B., Pettrilli, A., Klinglmayr, E., Chen, J., Lutz-Meindl, U., Knott, A.B. et al. (2010) S-Nitrosylation of DRP1 does not affect enzymatic activity and is not specific to Alzheimer’s disease. J. Alzheimer’s Dis. 20, S513–S526, https://doi.org/10.3233/JAD-2010-100552

158 Haun, F., Nakamura, T., Shiu, A.D., Cho, D.H., Tsunemi, T., Holland, E.A. et al. (2013) S-nitrosylation of dynamin-related protein 1 mediates mutant huntingtin-induced mitochondrial fragmentation and neuronal injury in Huntington’s disease. Antioxid. Redox Signal. 19, 1173–1184, https://doi.org/10.1089/ars.2012.4928

159 Gawlowska, T., Suarez, J., Scott, B., Torres-Gonzalez, M., Wang, H., Schwappacher, R. et al. (2012) Modulation of dynamin-related protein 1 (DRP1) function by increased O-linked-beta-N-acetylglucosamine modification (O-GlcNAc) in cardiac myocytes. J. Biol. Chem. 287, 30024–30034, https://doi.org/10.1074/jbc.M112.390682

160 Toyama, E.Q., Herzig, S., Courchet, J., Lewis, J.H., Loson, O.C., Hellberg, K. et al. (2016) Metabolism. AMP-activated protein kinase mediates mitochondrial fission in response to energy stress. Science 351, 275–281, https://doi.org/10.1126/science.aab4138
188 Vanstone, J.R., Yoon, G., Hudson, C., Frezza, C., Cipolat, S., Ferre, M., Amati-Bonneau, P., Tourmen, Y., Malthiery, Y. and Reynier, P. (2005) eOPA1: an online database for OPA1 mutations. J. Cell Sci. 127, 4954–4963, https://doi.org/10.1242/jcs.157321

187 Leboucher, G.P., Tsai, Y.C., Yang, M., Shaw, K.C., Zhou, M., Veenstra, T.D. et al. (2012) Stress-induced phosphorylation and proteasomal degradation of mitofusin 2 facilitates mitochondrial fragmentation and apoptosis. Mol. Cell 47, 547–557, https://doi.org/10.1016/j.molcel.2012.05.041

186 Chen, Y. and Dorn, II. (2016) PINK1-phosphorylated mitofusin 2 is a Parkin receptor for culling damaged mitochondria. Science 340, 471–475, https://doi.org/10.1126/science.1231031

185 Sugiura, A., Nagashima, S., Tokuyama, T., Amo, T., Matsuji, Y., Ishido, S. et al. (2013) MITOL regulates endoplasmic reticulum–mitochondria contacts via Mitofusin2. Mol. Cell 51, 20–34, https://doi.org/10.1016/j.molcel.2013.04.023

184 Sasaki, H. and Jensen, R.E. (2014) Ugo1p links the Fzo1p and Mgm1p presequence translocase to partner complexes. J. Cell Biol. 197, 595–604, https://doi.org/10.1083/jcb.201110047

183 Tondela, D., Santel, A., Schwarzr, R., Dames, S., Giese, K., Klippel, A. et al. (2004) Knockdown of MTP18, a novel phosphatidylinositol 3-kinase-dependent protein, affects mitochondrial morphology and induces apoptosis. J. Biol. Chem. 279, 31544–31555, https://doi.org/10.1074/jbc.M401336200

182 Tondela, D., Czaurdarna, F., Paulick, K., Schwarzr, R., Kaufmann, J. and Santel, A. (2005) The mitochondrial protein MTP18 contributes to mitochondrial fission in mammalian cells. J. Cell Biol. 168, 3049–3059, https://doi.org/10.1083/jcb.200410121

181 Morita, M., Prudent, J., Basu, K., Goyon, V., Katsumura, S., Hulea, L. et al. (2017) mTOR Controls Mitochondrial Dynamics and Cell Survival via MTPF1. Mol. Cell 67, 9229–9356, https://doi.org/10.1016/j.molcel.2017.08.013

180 Gebert, M., Schrempf, S.G., Mehnert, C.S., Heisswolf, A.K., Delpech, A., Leboucher, G.P. et al. (2012) Mgp2 promotes coupling of the mitochondrial presenence translocase to partner complexes. J. Cell Biol. 197, 595–604, https://doi.org/10.1083/jcb.201110047

179 Kijima, K., Numakura, C., Iizumino, H., Umetsu, K., Nezu, A., Shiiki, T. et al. (2005) Mitochondrial GTPase mitofusin 2 mutation in Charcot-Marie-Tooth neuropathy type 2A. Hum. Genet. 116, 23–27, https://doi.org/10.1007/s00439-004-1199-2

178 Cuesta, A., Pedrola, L., Sevilla, T., Garcia-Planells, J., Chumillas, M.J., Mayordomo, F. et al. (2002) The gene encoding ganglioside-induced differentiation-associated protein 1 is mutated in axonal Charcot-Marie-Tooth type 4A disease. Nat. Genet. 30, 22–25, https://doi.org/10.1038/ng798

177 Baxter, R.V., Ben Othmane, K., Rochelle, J.M., Ben Othmane, K., Rochelle, J.M., Leboucher, G.P. et al. (2004) Ganglioside-induced differentiation-associated protein-1 is mutant in Charcot-Marie-Tooth disease type 4A/Bq21. Nat. Genet. 30, 22–27, https://doi.org/10.1038/ng798

176 Boyer, O., Nevo, F., Plaisier, E., Funalot, B., Gribouval, O., Benoit, G. et al. (2011) INF2 mutations in Charcot-Marie-Tooth disease with glomerulopathy. N. Engl. J. Med. 365, 2377–2388, https://doi.org/10.1056/NEJMoa1109122

175 Voo, I., All, B.E., Udar, N., Silva-Garcia, R., Vance, J. and Small, K.W. (2003) Hereditary motor and sensory neuropathy type VI with optic atrophy. Am. J. Ophthalmol. 136, 670–677, https://doi.org/10.1016/S0002-9999(03)00390-8

174 Boyer, O., Benoit, G., Gribouval, O., Nevo, F., Tete, M.J., Danfatin, J. et al. (2011) Mutations in INF2 are a major cause of autosomal dominant focal segmental glomerulosclerosis. J. Am. Soc. Nephrol. 22, 239–245, https://doi.org/10.1681/ASN.2010050518

173 Zuchner, S., Nourreddine, M., Kennerson, M., Verhoek, E., Claey, K., De Jonghe, P. et al. (2005) Mutations in the pleckstrin homology domain of dynamin 2 cause dominant intermediate Charcot-Marie-Tooth disease. Nat. Genet. 37, 289–294, https://doi.org/10.1038/ng1514

172 Ferre, M., Amati-Bonneau, P., Tourmen, Y., Mathieu, Y. and Reyner, P. (2005) eOPA1: an online database for OPAT mutations. Hum. Mutat. 25, 423–428, https://doi.org/10.1002/humu.20161

171 Frezza, C., Cipolat, S., Martin de Brito, O., Micaroni, M., Bezoussenko, G.V., Rudka, T. et al. (2006) OPA1 controls apoptotic cristae remodeling independently from mitochondrial fusion. Cell 126, 177–189, https://doi.org/10.1016/j.cell.2006.06.025

170 Hudson, G., Amati-Bonneau, P., Blakely, E.L., Stewart, J.D., He, L., Schaefer, A.M. et al. (2008) Mutation of OPA1 causes dominant optic atrophy with external ophthalmoplegia, ataxia, deafness and multiple mitochondrial DNA deletions: a novel disorder of mtDNA maintenance. Brain 131, 329–337, https://doi.org/10.1093/brain/awm272

169 Amati-Bonneau, P., Valentino, M.L., Reyner, P., Gallardo, M.E., Bornstein, B., Boissiere, A. et al. (2008) OPA1 mutations induce mitochondrial DNA instability and optic atrophy ‘plus’ phenotypes. Brain 131, 338–351, https://doi.org/10.1093/brain/awm298

168 Yu-Wai-Man, P., Griffiths, P.G., Gorman, G.S., Lourenco, C.M., Wright, A.F., Auer-Grumbach, M. et al. (2010) Multi-system neurological disease is common in patients with OPA1 mutations. Brain 133, 771–786, https://doi.org/10.1093/brain/awq007

167 Olichon, A., Guillou, E., Deletrice, C., Landes, T., Arnaune-Pelloquin, L., Emorine, L.J. et al. (2006) Mitochondrial dynamics and disease, OPA1. Biochim. Biophys. Acta 1763, 500–509, https://doi.org/10.1016/j.bbamcr.2006.04.003

166 Yoon, G., Malam, Z., Paton, T., Marshall, C.R., Hyatt, E., Iakine, Z. et al. (2016) Lethal Disorder of Mitochondrial Fission Caused by Mutations in DN11L. J. Pediatr. 171, 313-6 e1–2, https://doi.org/10.1016/j.jpeds.2015.12.060

165 Vanstone, J.R., Smith, A.M., McBride, S., Naas, T., Holcik, M., Antoun, G. et al. (2016) DN11L-related mitochondrial fission defect presenting as refractory epilepsy. Eur. J. Hum. Genet. 24, 1084–1088, https://doi.org/10.1038/ejhg.2015.243
189 Braunisch, M.C., Gallwitz, H., Abicht, A., Diebold, I., Holinski-Feder, E., Van Maldergem, L. et al. (2018) Extension of the phenotype of biallelic loss-of-function mutations in SLC25A46 to the severe form of pontocerebellar hypoplasia type I. Clin. Genet. 93, 255–265, https://doi.org/10.1111/cge.13084

190 Wong, Y.C., Ysselstein, D. and Krainc, D. (2018) Mitochondria-lysosome contacts regulate mitochondrial fission via RAB7 GTP hydrolysis. Nature 554, 382–386, https://doi.org/10.1038/nature25486

191 Schmitt, K., Grimm, A., Dallmann, R., Gethinghaus, B., Restelli, L.M., Witzig, M. et al. (2018) Circadian control of DRP1 activity regulates mitochondrial dynamics and bioenergetics. Cell Metab. 27, 657e6–666e5, https://doi.org/10.1016/j.cmet.2018.01.011

192 Sugiura, A., McLelland, G.L., Fon, E.A. and McBride, H.M. (2014) A new pathway for mitochondrial quality control: mitochondrial-derived vesicles. EMBO J. 33, 2142–2156, https://doi.org/10.15252/embj.201488104