

Mitochondrial fusion and fission in cell life and death

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Abstract | Mitochondria are dynamic organelles that constantly fuse and divide. These processes (collectively termed mitochondrial dynamics) are important for mitochondrial inheritance and for the maintenance of mitochondrial functions. The core components of the evolutionarily conserved fusion and fission machineries have now been identified, and mechanistic studies have revealed the first secrets of the complex processes that govern fusion and fission of a double membrane-bound organelle. Mitochondrial dynamics was recently recognized as an important constituent of cellular quality control. Defects have detrimental consequences on bioenergetic supply and contribute to the pathogenesis of neurodegenerative diseases. These findings open exciting new directions to explore mitochondrial biology.

β -oxidation
Biochemical pathway of fatty acid catabolism in mitochondria and peroxisomes.

Mitochondria are semi-autonomous organelles that contain their own genome and protein synthesis machinery. Although most mitochondrial proteins are encoded by genes in the nucleus and are post-translationally imported into the organelle, the mitochondrial genome contains some genes that are required for respiratory activity. The most prominent role for mitochondria is to supply the cell with metabolic energy in the form of ATP generated by oxidative phosphorylation. Remarkably, mitochondria are indispensable for life even in organisms that do not depend on respiration because they are strictly required for the assembly of iron–sulphur clusters, which are essential cofactors of many mitochondrial and extra-mitochondrial enzymes. Furthermore, mitochondria are involved in many catabolic and anabolic reactions, including the citric acid cycle, β -oxidation of fatty acids and the biosynthesis of haem, certain phospholipids and other metabolites. In addition to their central role in various biochemical pathways, mitochondria are key regulators of apoptosis, and they participate in developmental processes and ageing.

The multitude of different functions of mitochondria is reflected in their structure. The double membrane-bound architecture of mitochondria was revealed in the 1950s by electron microscopy studies¹. The inner membrane is organized in characteristic folds, termed cristae, that protrude into the matrix and accommodate the respiratory chain complexes (FIG. 1a). However, the appearance of mitochondria as solitary bean-shaped organelles, as mostly seen in electron micrographs obtained from single sections of cells, turned out to be

misleading (however, this view is still conveyed in many text books). Remarkably, in the 1980s live cell microscopy studies showed that mitochondria are highly dynamic organelles that can build large interconnected intracellular networks² (FIG. 1b). In many eukaryotic cell types, mitochondria continuously move along cytoskeletal tracks and frequently fuse and divide. These concerted activities control mitochondrial morphology and intracellular distribution and determine their cell type-specific appearance.

The antagonistic and balanced activities of the fusion and fission machineries shape the mitochondrial compartment, and the dynamic behaviour of mitochondria allows the cell to respond to its ever-changing physiological conditions. A shift towards fusion favours the generation of interconnected mitochondria, whereas a shift towards fission produces numerous mitochondrial fragments (FIG. 1c). The large mitochondrial networks that are generated by fusion are beneficial in metabolically active cells, in which they contribute towards the dissipation of energy³. By contrast, in quiescent cells mitochondria are frequently present as numerous morphologically and functionally distinct small spheres or short rods⁴.

Research on mitochondrial fusion and fission (collectively termed mitochondrial dynamics) gained much attention in recent years, as it is important for our understanding of many biological processes, including the maintenance of mitochondrial functions, apoptosis and ageing⁵. Although most of the evolutionarily conserved core components of the mitochondrial fusion and fission

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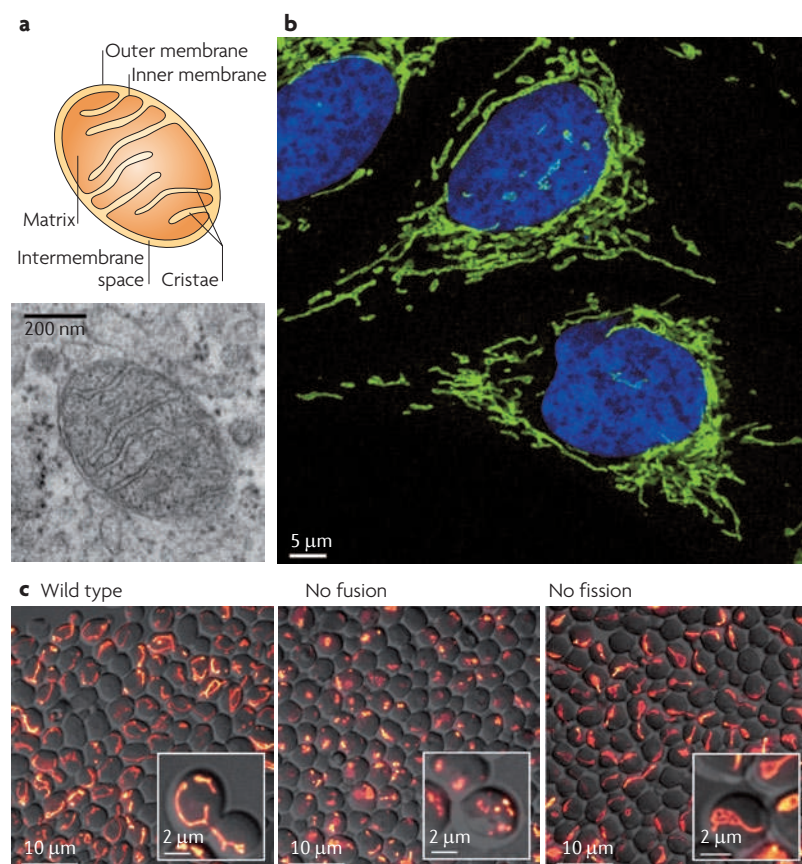


Figure 1 | Mitochondrial morphology. **a** | Mitochondria are double membrane-bound organelles with characteristic inner membrane folds, termed cristae. The schematic shows the structure of mitochondria. A transmission electron microscopy image of mitochondria in ultrathin sections of human fibroblast cells is also shown. **b** | In many cell types, mitochondria appear as long, tubular and sometimes branched structures that spread throughout the entire cytoplasm. Mitochondria (green) were stained in human osteosarcoma cells (U2OS) by indirect immunofluorescence using antibodies against the outer membrane protein TOM20. Nuclei (blue) were stained with DAPI (4',6-diamidino-2-phenylindole). Cells were analysed by confocal microscopy. **c** | Fusion and fission regulate mitochondrial morphology. Mitochondria are branched, tubular organelles in budding yeast (left panel). Mutants lacking the fusion component Fzo1 have numerous small mitochondrial fragments that are produced by mitochondrial fission in the absence of fusion (central panel). By contrast, mutants lacking the fission component Dnm1 contain highly interconnected net-like mitochondria (right panel). Mitochondria were stained by expression of mitochondrion-targeted green fluorescent protein from a plasmid. Cells were analysed by deconvolution fluorescence microscopy, and fluorescence micrographs (shown in false colour) were merged with differential interference contrast images. Image in part **a** courtesy of S. Geimer, Universität Bayreuth, Germany. Image in part **b** courtesy of S. Jakobs, Max-Planck Institut für Biophysikalische Chemie, Göttingen, Germany. Images in part **c** courtesy of J. Förtsch, Universität Bayreuth, Germany.

machineries have been described in the past 15 years (TABLE 1), more recent work revealed mechanistic insights into their molecular function^{6,7}. Moreover, the number of regulatory proteins and pathways that are known to integrate the dynamic behaviour of mitochondria into activities in the cell is steadily increasing. This Review describes the key mitochondrial proteins and the mechanisms by which they function, focusing on proteins that are conserved in yeast and animals. Three large GTPases and their interacting factors were found to constitute

the core machinery of mitochondrial dynamics. As our understanding of their function is most advanced in yeast, they are described from a mechanistic perspective in yeast, and common properties and differences with mammals are highlighted. I then discuss the various cellular functions of mitochondrial fusion and fission in yeast and mammals, including recent discoveries on mitochondrial DNA (mtDNA) stability and organellar quality control. Finally, I highlight the role of dysfunctions of mitochondrial dynamics in human diseases.

Mechanisms of mitochondrial fusion

Membrane fusion is a fundamental process in the life of eukaryotic cells. For example, transport vesicles fuse with the organelles of the secretory pathway, gametes fuse during fertilization, and enveloped viruses enter the host cytosol by fusion with endosomal membranes. The fusion machineries that have evolved to fit the needs of these different reactions are diverse, but they operate by common principles⁸. First, they bring membranes destined to be fused into close proximity and then they destabilize the bilayers by local induction of curvature. To achieve merging of lipid bilayers, membrane fusion proteins, such as soluble *N*-ethylmaleimide-sensitive fusion protein attachment protein receptors (SNAREs) and viral haemagglutinins, commonly contain heptad repeats that form inter- or intramolecular hairpin-like coiled-coils to draw the membranes into close apposition. These proteins also have hydrophobic domains inserted in these membranes to induce lipid bilayer deformation. Mitochondrial fusion is a particularly complex process, as mitochondria are double membrane-bound organelles and must coordinate the fusion of four membranes.

The mitochondrial fusion machinery. The first known mediator of mitochondrial fusion was identified in 1997 by molecular genetic analysis of the male sterile fuzzy onions (*fzo*) mutant in *Drosophila melanogaster*. The identified protein, FZO, is required for the fusion of mitochondria during spermatogenesis⁹. It is the founding member of a conserved protein family, termed mitofusins, that has members in yeast^{10,11}, worms¹² and mammals¹³. Even though mitochondrial fusion has been observed in plants, plant genomes apparently do not contain genes encoding FZO-related proteins (BOX 1). Mitofusins in yeast and metazoa share a similar domain structure (FIG. 2). They are large GTPases that contain two transmembrane regions in the mitochondrial outer membrane, with a short loop in the intermembrane space and the major parts of the protein facing the cytosol^{14,15}. Yeast Fzo1 contains three predicted heptad repeat regions. Mammals have two mitofusin isoforms, MFN1 and MFN2, both of which lack the most amino-terminal heptad repeat.

Mgm1 is a dynamin-related large GTPase that is essential for inner membrane fusion in yeast¹⁶. It has an N-terminal mitochondrial targeting sequence that is cleaved by matrix-processing peptidase (MPP) following import. A large Mgm1 isoform contains an N-terminal transmembrane domain that anchors the protein in the inner membrane, and its main part is located in the

SNARE

A protein belonging to a family of membrane proteins that mediate fusion of vesicles and organelles in the secretory pathway of eukaryotic cells.

Table 1 | **Yeast and mammalian proteins constituting the core machineries of mitochondrial dynamics and their interaction partners**

Yeast protein*	Mammalian protein*	Proposed function	Refs
Core components of the fusion machinery			
Fzo1	MFN1 and MFN2 [‡]	Outer membrane fusion	10,11,13–15,28,30,31
Mgm1	OPA1	Inner membrane fusion	16,19,27,29,32
Ugo1	Unknown	Outer membrane fusion and linking of Fzo1 and Mgm1	34–36
Core components of the fission machinery			
Dnm1	DRP1 (DLP1)	Outer membrane division	38,39,45,58
Fis1	FIS1	Outer membrane receptor for recruitment of Dnm1 or DRP1	40,42,52,53,59
Mdv1 and Caf4 [‡]	Unknown	Adaptor for Dnm1 binding to Fis1 and nucleator for Dnm1 oligomerization	41,43,44,46,47
Unknown	MFF	Putative alternative DRP1 recruitment factor	56
Accessory components of fusion and fission			
Pcp1 (Rbd1 and Mdm37)	PARL	Processing of Mgm1 or OPA1	17,18,21,48,67
Unknown	Intermembrane space and matrix AAA proteases	Processing of OPA1	22–25
Unknown	OMA1	Processing of OPA1	24,26
Num1	Unknown	Cell cortex anchor with Dnm1	48–50
Mdm36	Unknown	Formation of Num1–Dnm1 cell cortex anchor	48,50
Regulatory components of fusion and fission			
Mdm30	Unknown	Ubiquitin ligase for Fzo1	48,64–66
Unknown	MARCH5 (MITOL)	Ubiquitin ligase for MFN1, MFN2, DRP1 and FIS1	69–72
Unknown	MAPL	SUMO ligase for DRP1	73
Unknown	SEN5	SUMO protease for mitochondrial proteins	74
Unknown	CDK1–cyclin B	Cell cycle-dependent phosphorylation of DRP1	75
Unknown	PKA	cAMP-dependent phosphorylation of DRP1	76
Unknown	CaMKI α	Calcium-dependent phosphorylation of DRP1	77
Unknown	Calcineurin	Calcium-dependent dephosphorylation of DRP1	76,78
Unknown	MIB	Negative regulator of mitofusins	79
Unknown	PGC1 β	Increase of MFN2 transcription	80
Unknown	BAX	MFN2 complex assembly	81

CaMKI α ; Ca²⁺/calmodulin-dependent protein kinase I α ; cAMP, cyclic AMP; CDK1, cyclin-dependent kinase 1; DRP1; dynamin-related protein 1; Fis1, mitochondrial fission 1; MAPL, mitochondrial-anchored protein ligase; Mdm, mitochondrial distribution and morphology; Mdv1, mitochondrial division protein 1; MFN, mitofusin; MFF, mitochondrial fission factor; Num1, nuclear migration 1; OPA1, optic atrophy protein 1; PARL, presenilins-associated rhomboid-like; PGC1 β ; peroxisome proliferator-activated receptor- γ coactivator 1 β ; PKA, cAMP-dependent protein kinase; SEN5, sentrin-specific protease 5; SUMO, small ubiquitin-like modifier.

*Alternative names are provided in brackets. [‡]Paralogues in the same organism.

Haemagglutinin

A glycoprotein of enveloped viruses, such as influenza virus. Haemagglutinins mediate fusion of the viral envelope with endosomal membranes to release the viral particle into the host cytosol.

Heptad repeat

A structural protein motif that is commonly found in coiled coils that contain two or more α -helices coiled together forming a rope-like structure.

intermembrane space. A fraction of Mgm1 molecules is processed further during import by the rhomboid-related membrane protease Pcp1, generating a short isoform that lacks the transmembrane anchor^{17,18}. Both isoforms contain a GTPase domain, a GTPase effector domain and several heptad repeats (FIG. 2). The mammalian Mgm1 orthologue, optic atrophy protein 1 (OPA1), and related proteins in worms and flies have also been shown to be required for mitochondrial fusion^{12,19,20}. OPA1 is present in eight isoforms that are generated by alternative splicing and alternative processing at two cleavage sites that are located between the N-terminal transmembrane domain and the first heptad repeat (FIG. 2). Several proteases have been implicated in alternative processing of mammalian OPA1, including the rhomboid-related protease presenilins-associated rhomboid-like (PARL)²¹, AAA proteases in the matrix and the intermembrane

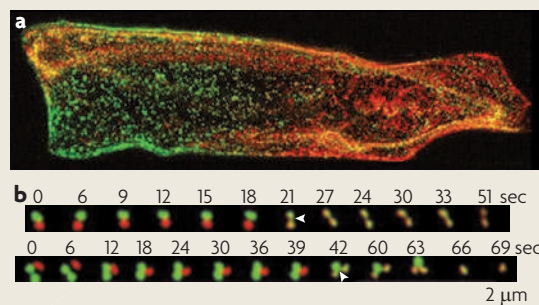
space^{22–25}, and the inner membrane peptidase OMA1 (also known as MPRP1)^{24,26}.

Several lines of evidence suggest that Fzo1 together with Mgm1, or mitofusins together with OPA1, are the core components of the mitochondrial fusion machinery. First, mutant cells contain fragmented mitochondria in yeast^{10,11,27} and mammals^{28,29}. Second, mitochondria in fused cells that lack Fzo1, mitofusins, Mgm1 or OPA1 cannot mix their matrix contents, indicating a lack of fusion^{11,19,27,28}. Third, mitochondria isolated from yeast mutants lacking Fzo1 or Mgm1 are unable to fuse *in vitro*^{16,30}. And fourth, mitofusins, Mgm1 and OPA1 possess the domains that are predicted to be present in a fusogen: these are transmembrane domains and heptad repeats, plus a GTPase domain that could provide biomechanical energy to overcome the energy barrier of lipid bilayer mixing.

Box 1 | Mitochondrial dynamics in plants

Equivalents of metazoan or fungal mitochondrial fusion proteins have not been found in the fully sequenced genomes of higher plants or eukaryotic algae. However, plant mitochondria are also dynamic organelles, as was shown using a mitochondrion-targeted variant of the switchable fluorescent protein Kaede in onion epidermal cells¹²⁸. Kaede fluorescence changes from green to red following irradiation with ultraviolet light. After photoconversion of a subpopulation of mitochondria, red-coloured mitochondria fuse with mitochondria containing non-photoconverted green Kaede, and fused mitochondria appear yellow in merged fluorescence micrographs. The figure part **a** shows an onion epidermal cell containing fused mitochondria; part **b** shows time courses of individual mitochondria captured in the process of fusion (arrowheads mark fusion events). The identity of the mediators of mitochondrial fusion in plants is currently not known.

Similarly to yeast and humans, mitochondrial fission in *Arabidopsis thaliana* is mediated by the dynamin-related proteins DRP3A and DRP3B (formerly known as ADL2a and ADL2b)^{129,130}. Furthermore, a possible mitochondrial fission 1 (Fis1) orthologue, BIGYIN, was shown to control mitochondrial size and number in *A. thaliana*¹³¹. However, *A. thaliana* does not have genes related to mitochondrial division protein 1 (MDV1). Instead, the plant-specific protein elongated mitochondria 1 (ELM1) was recently proposed to recruit DRP3A and DRP3B to mitochondria, possibly cooperating with BIGYIN¹³². Remarkably, in some primitive algae and other protists mitochondria apparently retained the division machinery of their α -proteobacterial endosymbiotic ancestors. For example, homologues of the bacterial division protein FtsZ are targeted to mitochondria in the chromophyte alga *Mallomonas splendens*¹³³ and the red alga *Cyanidioschyzon merolae*¹³⁴. We are only beginning to discover the diversity of mitochondrial fusion and fission machineries in plants and lower eukaryotes. Image in part **a** courtesy of S. Arimura, University of Tokyo, Japan. Image in part **b** reproduced, with permission, from REF. 128 © (2004) National Academy of Sciences, USA.



These observations can be integrated into a hypothetical model of mitochondrial fusion. It is conceivable that early during fusion two mitochondria approaching each other are tethered in a docking step. Consistently, the carboxy-terminal heptad repeats of mammalian MFN1 have been shown to form an intermolecular antiparallel coiled coil that may tether adjacent mitochondria prior to fusion³¹. Coiled coil formation by mitofusins might then draw the membranes close together and initiate lipid bilayer mixing, and the GTPase could provide biomechanical energy for outer membrane fusion. The first mechanistic insights into the role of Mgm1 in inner membrane fusion came from the analysis of yeast mutant mitochondria *in vitro*. After the completion of outer membrane fusion, Mgm1 is required *in trans* on both inner membranes of the fusion partners. Certain *mgm1* mutant alleles show a specific defect in inner membrane tethering, whereas others are defective in inner membrane fusion, suggesting that Mgm1 participates in both processes¹⁶. Interestingly, studies using purified Mgm1 variants reconstituted with liposomes showed that only the short Mgm1 isoform, which lacks the transmembrane region, has GTPase activity, and that its GTPase is activated in heterotypic complexes containing the membrane-bound long isoform. Thus, the long Mgm1 isoform is proposed to tether opposing inner membranes and harness GTPase-dependent conformational changes of the short isoform to initiate lipid bilayer mixing of the inner membrane³².

Coordination of outer and inner membrane fusion. Dissipation of the membrane potential or mutations in Mgm1 or OPA1 selectively block inner membrane fusion. Under these conditions, outer membrane fusion

proceeds in the absence of inner membrane fusion^{16,30,33}. Thus, the fusion machineries in the mitochondrial outer and inner membranes can operate independently of each other. However, it is conceivable that under normal conditions outer membrane fusion is coordinated with inner membrane fusion. Yeast mutants carrying insertions between the transmembrane regions of Fzo1 show a specific loss of Fzo1 interactions with the inner membrane and severe defects in mitochondrial fusion. Thus, the intermembrane space loop of Fzo1 plays an important part in the coordination of double-membrane fusion¹⁴. Furthermore, Ugo1, an outer membrane protein that is essential for mitochondrial fusion in yeast³⁴, also participates in connecting the outer and inner membrane fusion machineries. It contains three transmembrane domains and two mitochondrial carrier family signatures of unknown function³⁵ (FIG. 2). Ugo1 physically interacts with both Fzo1 and Mgm1 (REF. 36). Intriguingly, temperature-sensitive *ugo1* alleles revealed specific defects in outer or inner membrane fusion at a post-tethering step³⁵. This phenotype is compatible with a role for Ugo1 as a linker that connects Fzo1 with Mgm1 and coordinates double-membrane fusion. Structurally or functionally related Ugo1 equivalents in higher eukaryotes have not been identified.

Mechanisms of mitochondrial fission

Dynamin superfamily members are versatile large GTPases that mediate various membrane remodelling processes in eukaryotic cells. Mgm1 and OPA1, and in particular Fzo1 and mitofusins, are distantly related dynamin superfamily members. Although these proteins function in membrane fusion, classical dynamins

Dynamin

A large GTPase involved in membrane scission events.

Rhomboid

The founding member of a conserved family of intramembrane Ser proteases that have their active sites buried in the plane of the membrane.

AAA proteases

Large multisubunit proteases that belong to the superfamily of ATPases that are associated with diverse cellular activities.

Liposome

Artificial lipid bilayer vesicle composed of membrane lipids.

Mitochondrial carrier family signature

A protein sequence motif that is commonly found in mitochondrial carrier proteins that function in the transport of metabolites and other biomolecules across the mitochondrial inner membrane.

Tetratricopeptide repeat motif

A motif that consists of a degenerate 34 amino acid sequence and functions as a protein–protein interaction module in various functionally different proteins.

WD40 repeat

A protein-binding motif that typically contains several regions of about 40 amino acids with conserved Trp–Asp dipeptides that form characteristic β -propeller structures.

are typically involved in membrane scission events in vesicle budding pathways. For example, the *D. melanogaster* protein shibire, the first well-characterized dynamin family member, pinches off newly formed endocytic vesicles from the plasma membrane to release them into the cytosol. Classical dynamins assemble into higher oligomeric structures that form rings and spirals around membranes. These spirals are thought to sever the enclosed membranes following GTP hydrolysis through the mechanoenzymatic activity of dynamin³⁷. Dynamin-related proteins have similar roles in the division of membrane-bound organelles, including endosomes, peroxisomes and mitochondria.

The mitochondrial fission machinery. A dynamin-related protein, termed Dnm1 in yeast and dynamin-related protein 1 (DRP1) in mammals, is the master regulator of mitochondrial division in most eukaryotic organisms. It is a soluble protein containing an N-terminal GTPase, a middle domain and a C-terminal GTPase effector domain that is involved in self-assembly (FIG. 2). Humans have an additional alternatively spliced brain-specific isoform with an insertion between the middle domain and the GTPase effector domain³⁸. Cells lacking Dnm1 or DRP1 contain highly interconnected mitochondrial nets that are formed by ongoing fusion in the absence of fission activity^{38,39}.

The function of the mitochondrial fission machinery is best understood in yeast. Recruitment of Dnm1 from the cytosol and assembly in punctate structures on the mitochondrial surface depends on two partner proteins, mitochondrial fission 1 (Fis1) and mitochondrial division protein 1 (Mdv1)^{40,41}. Fis1 is a small tail-anchored protein in the outer membrane. Its N-terminal domain faces the cytosol, where it forms a six-helix bundle with tandem tetratricopeptide repeat motifs (TPR) that provide an interface for interaction with the adaptor protein Mdv1 (REF. 42). Mdv1 contains an N-terminal extension for Fis1 binding, a heptad repeat region mediating homo-oligomeric interactions and a C-terminal WD40 repeat domain that interacts with Dnm1 (REF. 43) (FIG. 2).

Recent *in vitro* studies using purified proteins revealed mechanistic insights into the role of Mdv1 as a dynamin effector that mediates the assembly of Dnm1. Mdv1 binds preferentially to the GTP-bound form of Dnm1 and stimulates its self-assembly; therefore, Mdv1 functions as a nucleator for Dnm1 polymerization on mitochondria by inducing or stabilizing favourable Dnm1 conformations. In addition, Mdv1 provides a functional scaffold that stabilizes oligomeric Dnm1 assemblies⁴⁴. Intriguingly, GTP-bound Dnm1 was found to self-assemble into extended helical structures that can constrict artificial liposomes *in vitro*. These spirals have a diameter of 100 nm and fit in mitochondrial constrictions at division sites, which have a diameter of ~100 nm *in vivo*⁴⁵. Taken together, these data suggest the following model of mitochondrial division in yeast. First, Fis1 recruits Mdv1 from the cytosol. Membrane-associated Mdv1 then nucleates the assembly of Dnm1–GTP oligomers on the mitochondrial surface. Dnm1–GTP oligomers proceed to form spirals that are eventually wrapped around the organelle. Finally, Dnm1 spirals sever the mitochondrial membranes following GTP hydrolysis in a manner that is probably similar to the action of classical dynamins in vesicular budding pathways.

The Fis1–Mdv1–Dnm1 complex is important for mitochondrial division, but Fis1 can also cooperate with the Mdv1 paralogue Caf4, which has the same domain structure as Mdv1 (FIG. 2), to recruit Dnm1 to mitochondria. Even though Caf4 is dispensable for fission in the presence of Mdv1, it maintains residual fission activity in mutants lacking Mdv1 (REF. 46). Furthermore, it seems to be important to establish the orientation of a subset of Dnm1 assemblies towards the cell cortex⁴⁷. The biological importance of the Fis1–Caf4–Dnm1 complex is currently unclear; however, the attachment of mitochondria to the cell cortex through a third Dnm1-containing complex involving nuclear migration 1 (Num1) is known to be important for mitochondrial division. Num1 is a large cell cortex-anchored protein that was known to function in nuclear segregation. In a systematic genome-wide screen of yeast deletion mutants it was later found that Num1 is also important for maintaining mitochondrial morphology⁴⁸. Num1 colocalizes with a subset of mitochondrion-associated Dnm1 assemblies that are mutually exclusive with those containing Fis1 and Mdv1 (REF. 49). Formation of Dnm1–Num1 complexes depends on the mitochondrion-associated protein

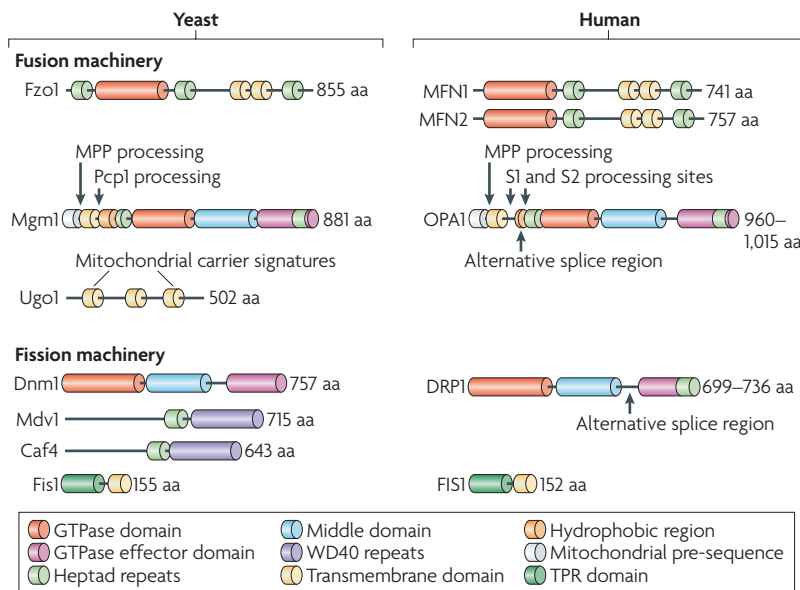


Figure 2 | Domain structures of mitochondrial fusion and fission components.

The core components of the mitochondrial fusion machinery in yeast are Fzo1 (mitofusin 1 (MFN1) and MFN2 in mammals) in the outer membrane and Mgm1 (optic atrophy protein 1 (OPA1) in mammals) in the inner membrane. These proteins are connected by the yeast-specific outer membrane protein Ugo1. The soluble protein Dnm1 (dynamin-related protein 1 (DRP1) in mammals) is recruited to mitochondria by the outer membrane protein mitochondrial fission 1 (Fis1; FIS1 in mammals). Two yeast-specific proteins, mitochondrial division protein 1 (Mdv1) and Caf4, serve as adaptors. The lengths of the yeast and human proteins (numbers of amino acids) and important processing and splice sites are indicated. Matrix-processing peptidase (MPP) removes matrix-targeting sequences following import; Pcp1 is a membrane protease involved in alternative processing of Mgm1; OPA1 is processed by different proteases, at two sites S1 and S2. Proteins are not drawn to scale. TPR, tetratricopeptide repeat.

Mdm36 (mitochondrial distribution and morphology 36). As mitochondria are highly motile and lose their localization to the cell periphery in cells lacking Num1 or Mdm36, it is thought that these proteins together with Dnm1 form cell cortex anchors that immobilize parts of the mitochondrial network⁵⁰. Interestingly, it was shown that membrane scission by classical dynamins is facilitated by the generation of tension on the membrane⁵¹. Thus, it is conceivable that mitochondrial cortex anchors together with cytoskeleton-dependent forces generate tension on mitochondrial membranes to promote mitochondrial fission by Dnm1 (REF. 50). It will be interesting to see whether mitochondrial division is linked to motility in other cell types.

Mammalian FIS1 interacts with DRP1 and apparently has a similar role in mitochondrial fission to its yeast counterpart, as FIS1 overexpression promotes mitochondrial fragmentation and FIS1 depletion produces interconnected mitochondrial nets^{52,53}. However, Mdv1 homologues have not been identified in metazoans which indicates significant differences between the metazoan and yeast mitochondrial division machineries. Furthermore, knockdown of human FIS1 does not affect the distribution of DRP1 in mitochondria⁵⁴, and deletion of the two *FIS1* homologous genes in *Caenorhabditis elegans* does not produce a strong mitochondrial fission phenotype⁵⁵, suggesting that additional pathways of DRP1 recruitment exist in metazoans. One possible candidate for an alternative fission factor is mitochondrial fission factor (MFF), a tail-anchored protein that is conserved in metazoans but does not exist in yeast. MFF contains heptad repeats and a C-terminal transmembrane domain that is embedded in the outer membrane. Depletion of MFF attenuates mitochondrial division, both in mammalian and *D. melanogaster* cells. Interestingly, MFF and FIS1 exist in separate complexes, suggesting that they have different roles in mitochondrial division⁵⁶.

A separate division machinery in the inner membrane?

Only little is known about division of the mitochondrial inner membrane. It is conceivable that Mdv1-coordinated assembly of Dnm1 produces spirals that constrict the organelle from its normal diameter of ~300 nm to ~100 nm, as has been observed with purified Dnm1 on liposomes^{44,45}. Following GTP hydrolysis, constriction of Dnm1 spirals might then sever both mitochondrial membranes at the same time. However, live cell microscopy of yeast and *C. elegans* showed that mitochondrial constriction and separation of matrix compartments can proceed independently of Dnm1 or DRP1 (REFS 57–59). Thus, it is possible that there is a separate machinery for constriction and/or division of the inner membrane. One possible candidate in yeast is Mdm33, a heptad repeat-containing inner membrane protein. Mutants lacking Mdm33 have extremely elongated and stretched mitochondria, indicating a lack of division activity. Overexpression of Mdm33 leads to mitochondrial fragmentation and induces the formation of inner membrane septae, possibly as a consequence of increased inner membrane division activity⁶⁰. Although

Mdm33 does not have homologues in higher eukaryotes, the inner membrane protein MTP18 has been postulated to have a role in fission in mammals. Overexpression of MTP18 induces fragmentation of mitochondria, whereas depletion produces highly fused mitochondria, a phenotype consistent with a role in inner membrane fission⁶¹. Clearly, more work is required to define the roles of Mdm33 and MTP18 in mitochondrial dynamics.

Regulators of mitochondrial dynamics

Mitochondrial fusion and fission are antagonistic activities^{62,63}. Thus, the rates of fusion and fission must be tightly controlled to keep the right balance required for the maintenance of mitochondrial morphology or to shift this balance to adapt the degree of mitochondrial interconnectivity to changing physiological conditions. Owing to their central role in mitochondrial fusion and fission, Fzo1, Mgm1 and Dnm1 in yeast and mitofusins, OPA1 and DRP1 in mammals are prime targets for regulatory pathways. Although the core machineries of mitochondrial dynamics are highly conserved, the mechanisms to control their activities seem to be more diverse in different organisms and cell types (FIG. 3).

In yeast, Fzo1 levels are controlled by the F-box protein Mdm30. Mutants lacking Mdm30 accumulate excess Fzo1 and contain fusion-incompetent mitochondria⁶⁴. Mdm30 is a subunit of a Skp1–cullin–F-box (SCF) ubiquitin ligase, which promotes ubiquitylation and degradation of Fzo1 by the proteasome⁶⁵. This activity is required to control steady-state levels of Fzo1 and to maintain fusion-competent mitochondria in vegetative cells. Intriguingly, Mdm30-dependent ubiquitylation and degradation is reduced in GTPase-deficient *fzo1* mutants. This observation suggests that the Fzo1 GTPase cycle is intimately linked to ubiquitylation and that Fzo1 degradation is an important new aspect in the fusion pathway⁶⁶.

An attractive hypothesis, termed ‘alternative topogenesis’, proposes that processing of Mgm1 by Pcp1 regulates mitochondrial fusion in response to matrix ATP levels⁶⁷. Newly synthesized Mgm1 is imported into mitochondria through protein translocases that reside in the mitochondrial outer and inner membranes. During import, the mitochondrial pre-sequence is removed by MPP. Two pathways are then possible. The first hydrophobic region might insert into the inner membrane, generating the membrane-anchored long isoform. Alternatively, Mgm1 might be translocated further into the matrix, thereby exposing the second hydrophobic region to the membrane protease Pcp1. This enables cleavage by Pcp1, generating the short Mgm1 isoform, which is released into the intermembrane space. As import of Mgm1 is ATP dependent, matrix ATP levels could directly determine the ratio of Mgm1 isoforms. At low ATP levels import would be slow, allowing the long isoform enough time to insert into the inner membrane before the Pcp1 processing site becomes accessible. By contrast, high ATP levels would favour fast import and thus promote further translocation to allow Pcp1 processing. Because both isoforms are required for mitochondrial fusion, this mechanism could link mitochondrial fusion activity to mitochondrial energy levels.

F-box protein

A protein that contains an F-box as a protein interaction domain. Most F-box proteins are substrate recognition subunits of SCF ubiquitin ligases and have roles in ubiquitin-dependent protein degradation.

Ubiquitin ligase

An enzyme that mediates the covalent attachment of ubiquitin to substrate proteins to label them for degradation by the proteasome or other regulatory pathways. This process is termed ubiquitylation.

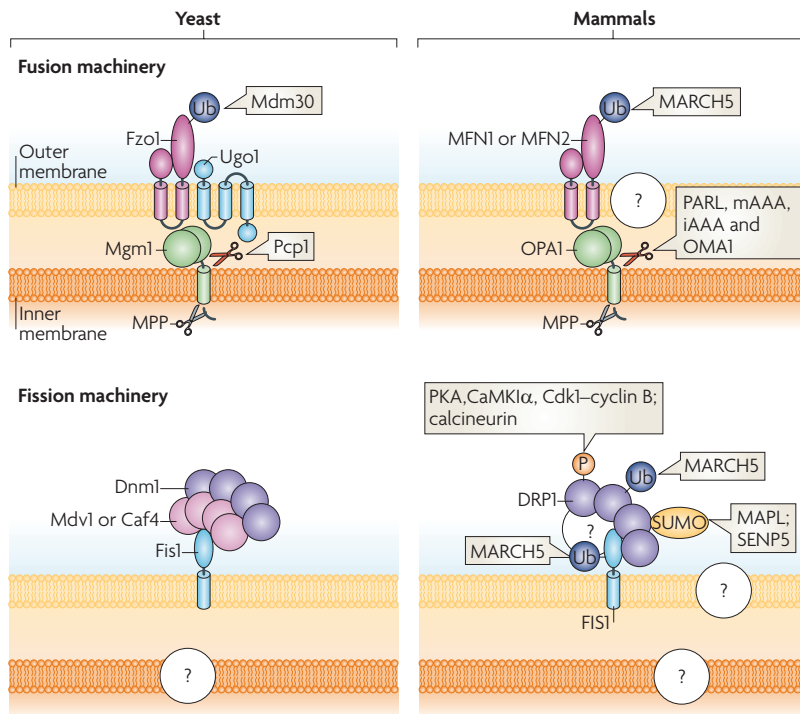


Figure 3 | Assembly and post-translational modifications of mitochondrial fusion and fission machineries. Mitochondrial fusion and fission proteins assemble in higher order complexes in the mitochondrial membranes. The stoichiometry of these multisubunit complexes is not exactly known. Several post-translational modifications regulate the activity of the fusion and fission machineries. The mitochondrial targeting sequence of Mgm1 or optic atrophy protein 1 (OPA1) is cleaved by matrix processing peptidase (MPP) following import. Alternative processing by Pcp1 in yeast or by presenilins-associated rhomboid-like (PARL), matrix AAA proteases (mAAA), intermembrane AAA proteases (iAAA) or OMA1 in mammals generates a soluble short isoform that associates with the inner membrane-anchored long isoform in the intermembrane space. In yeast, Fzo1 is ubiquitinated by Mdm30 (mitochondrial distribution and morphology 30). The mitochondrial ubiquitin ligase MARCH5 ubiquitinates mitofusins, dynamin-related protein 1 (DRP1) and mitochondrial fission 1 (FIS1) in mammals. DRP1 is sumoylated by mitochondrial-anchored protein ligase (MAPL) and desumoylated by sentrin-specific protease 5 (SENP5). Three kinases, cyclin-dependent kinase 1 (CDK1)–cyclin B, cAMP-dependent protein kinase (PKA) and Ca^{2+} /calmodulin-dependent protein kinase Ia (CaMKI α) phosphorylate DRP1, and calcineurin dephosphorylates DRP1. Additionally, yet unknown, factors might exist that coordinate division of the inner membrane, connect mitofusins with OPA1, coordinate DRP1 binding to FIS1 or recruit DRP1 to mitochondria in a FIS1-independent manner. These are indicated by question marks. Mdv1; mitochondrial division protein 1.

Small ubiquitin-like modifier
A small protein that is covalently attached to and removed from other proteins to modify their activity.

Nucleoid
A compact structure that contains DNA and proteins. Mitochondrial nucleoids contain several copies of the mitochondrial genome and are attached to the inner membrane.

Processing of OPA1 regulates mitochondrial fusion activity in mammalian cells. For example, generation of the short OPA1 isoform along with fragmentation of mitochondria is favoured at low membrane potential, low ATP levels or during apoptosis^{22,23,25,68}. Although the alternative topogenesis model is useful to interpret observations in yeast, processing of OPA1 in higher organisms seems to be more complex. Many proteases are involved, including PARL, several AAA proteases and OMA1, and certain splice variants are differentially processed^{22–26}. It is possible that tissue-specific expression of OPA1-cleaving proteases and/or splice variants contributes to the complex pattern of OPA1 processing. However, recent studies suggest that at least some specific processing steps fulfil a distinct function. Cleavage

by the inner membrane protease OMA1 is induced in impaired mitochondria with low membrane potential^{24,26}. As the long and short OPA1 isoforms are both required for fusion²⁵, complete conversion of OPA1 to the short isoform by OMA1 shuts off the fusion machinery of dysfunctional mitochondria. This activity could contribute to quality control by preventing fusion of defective mitochondria with the mitochondrial network^{24,26}. Importantly, processing by OMA1 is not restricted to newly imported OPA1, but allows the cell a more rapid stress response through complete cleavage of all long OPA1 molecules that are present.

Many additional pathways have been discovered that regulate the activities of the fusion and fission machineries in mammalian cells (TABLE 1). MARCH5 (also known as MITOL), a ubiquitin ligase in the outer membrane, associates with and ubiquitinates DRP1, FIS1 and mitofusins^{69–72}. Loss of MARCH5 is associated with mitochondrial elongation and triggers cell senescence⁷². Mitochondrial-anchored protein ligase (MAPL) is a mitochondrion-anchored small ubiquitin-like modifier (SUMO) ligase that attaches SUMO to DRP1 to stimulate mitochondrial fission⁷³. Removal of SUMO from DRP1 involves sentrin-specific protease 5 (SENP5), a SUMO protease that recognizes several mitochondrial targets⁷⁴. Furthermore, the activity of DRP1 can be reversibly modified by phosphorylation. Three protein kinases have been identified that phosphorylate different DRP1 Ser residues: cyclin-dependent kinase 1 (CDK1)–cyclin B⁷⁵, cAMP-dependent protein kinase (PKA)⁷⁶ and Ca^{2+} /calmodulin-dependent protein kinase Ia (CaMKI α)⁷⁷. The phosphatase calcineurin regulates mitochondrial morphology by dephosphorylating DRP1 in response to Ca^{2+} signals^{76,78}. Moreover, MIB was identified as a MFN1-interacting protein that attenuates mitochondrial fusion by an unknown mechanism⁷⁹. In addition, mitochondrial dynamics can be modulated at the transcriptional level⁸⁰ or by the regulated assembly of mitofusin complexes⁸¹. Thus, mammalian cells possess a large repertoire of different regulatory factors to modulate mitochondrial dynamics in response to various signals.

Functions of mitochondrial dynamics

Mitochondria cannot be generated *de novo*; instead, they proliferate by growth and division of pre-existing organelles. They contain their own genome and protein translation machinery. mtDNA is present in multiple copies and packed into compact particles, termed nucleoids. It encodes ribosomal RNAs, tRNAs and some proteins required for respiration. However, most mitochondrial proteins are encoded by nuclear genes and synthesized by cytosolic ribosomes. Mitochondrial biogenesis involves the import of nucleus-encoded proteins from the cytosol, the incorporation of mitochondrion-synthesized and imported membrane lipids, the amplification of the mitochondrial genome and the translation of mitochondrion-encoded proteins^{82–84}. Damaged and surplus organelles are removed by autophagy. During their life cycle, mitochondria fuse with each other and split apart again (FIG. 4a); fusion serves to mix and

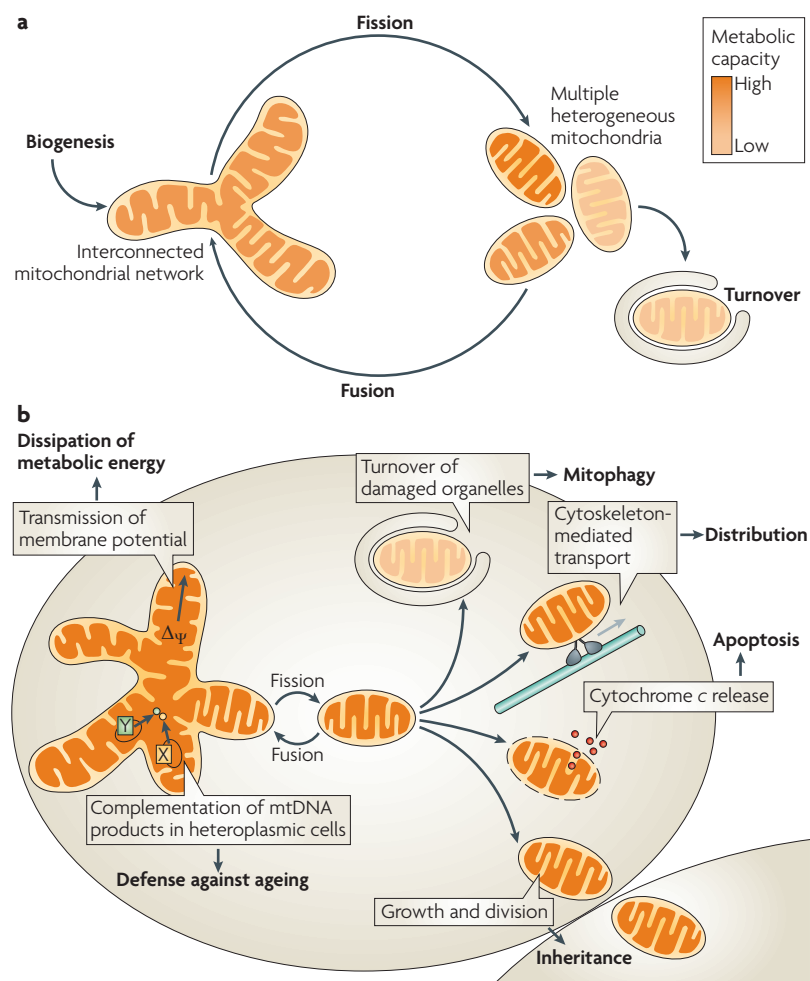


Figure 4 | Biological functions of mitochondrial dynamics. **a** | The mitochondrial life cycle starts with growth and division of pre-existing organelles (biogenesis) and ends with degradation of impaired or surplus organelles by mitophagy (turnover). In between, mitochondria undergo frequent cycles of fusion and fission that allow the cell to generate multiple heterogeneous mitochondria or interconnected mitochondrial networks, depending on the physiological conditions. **b** | Fusion and fission of mitochondria are important for many biological functions. Division is required for inheritance and partitioning of organelles during cell division, for the release of pro-apoptotic factors from the intermembrane space, for intracellular distribution by cytoskeleton-mediated transport and for turnover of damaged organelles by mitophagy. Fused mitochondrial networks are important for the dissipation of metabolic energy through transmission of membrane potential along mitochondrial filaments and for the complementation of mitochondrial DNA (mtDNA) gene products in heteroplasmic cells to counteract decline of respiratory functions in ageing (X and Y depict alleles of different mitochondrial genes).

unify the mitochondrial compartment, whereas fission generates morphologically and functionally distinct organelles. These processes have important consequences for mitochondrial functions in cell life and death (FIG. 4b).

Mitochondrial inheritance. Mitochondria are essential organelles that must be inherited during cell division. It is obvious that the number of mitochondria must increase during proliferation of cells. Accordingly, the mitochondrial network of mammalian interphase cells in culture was observed to fragment before the cells

enter mitosis and undergo cytokinesis^{75,85}. This allows partitioning of organelles to the daughter cells in a stochastic manner. Cell cycle-dependent mitochondrial morphology changes are much less pronounced in yeast. Instead, mitochondria are inherited in an ordered manner by cytoskeleton-dependent bud-directed transport⁸⁶. Surprisingly, yeast mutants lacking Dnm1 do not show a significant growth defect, even though their interconnected mitochondrial network must split in two parts during cell division. Similarly, knockout of *Drp1* does not affect the progression of cytokinesis in mouse embryonic fibroblasts⁸⁵. It is not known whether mitochondrial division in mutant cells is mediated by mechanical forces imposed on the organelle during cytokinesis or by an as-yet-unidentified Dnm1- or DRP1-independent division machinery. However, mice that lack mitofusins²⁸ or DRP1 (REFS 85,87) die before birth, which indicates that mitochondrial dynamics is essential in mammalian development.

Mitochondrial fusion is important for inheritance and maintenance of mtDNA. In yeast, fusion-defective mutants rapidly lose their mitochondrial genome and consequently show defects in respiration⁸⁸. This is probably because fragmentation of mitochondria produces multiple small organelles, most of which lack mtDNA, so partitioning of these organelles to daughter cells produces a significant number of progeny lacking mtDNA. As a result, mitochondrial genomes are lost from the population after several generations.

Disruption of fusion in mammalian cells also leads to mitochondrial heterogeneity and dysfunction, possibly as a consequence of nucleoid loss in individual mitochondria^{89,90}. Thus, it seems that fusion serves as a fundamental mechanism to maintain a mitochondrial population with a full complement of nucleus- and mitochondrion-encoded gene products. Although mitochondrial fission inevitably generates organelles lacking nucleoids, fusion ensures that the mitochondrial genome and gene products are replenished before functionality is lost.

Mitochondrial distribution and morphology. Cells defective in mitochondrial division contain highly interconnected net-like mitochondria that typically accumulate in restricted areas, leaving large parts of the cell devoid of mitochondria. Proper mitochondrial distribution depends on division to split the mitochondrial network into transportable units. Obviously, this is particularly important in large and extended cells, such as neurons. Accordingly, DRP1 and OPA1 are crucial to establish proper mitochondrial content in dendrites. This, in turn, is essential for the maintenance of dendritic spines and synapses, which are neuronal structures with a particularly high energy demand⁹¹. Moreover, *Drp1*-knockout mice have severe developmental abnormalities, particularly in the forebrain and the cerebellum^{85,87}. Intriguingly, mutant neurons in primary cell culture show an accumulation of mitochondria in the cell body, with only a few clumped and irregularly distributed mitochondria in neurites; this indicates that DRP1 deficiency impedes proper

mitochondrial distribution⁸⁵. Mice carrying conditional *Mfn2*-knockout alleles show highly specific degeneration of Purkinje neurons. Mitochondria in these mutant cells are fragmented and fail to distribute to the long and branched neurite processes, indicating that fusion may also influence mitochondrial distribution⁹⁰. A possible explanation is that most mutant mitochondria have defects in respiration because they lack mtDNA due to an inheritance defect. This may be sensed by the neuronal transport system, which may then transport inactive mitochondria preferentially towards the cell body⁹⁰.

In other cell types, fused mitochondrial networks act as electrically united systems that transmit the membrane potential generated by the proton pumps of the respiratory chain⁹². This mechanism was proposed to play an important part in the dissipation of metabolic energy in muscle cells. In these unusually large cells, mitochondrial filaments connect a dense layer of mitochondria in the oxygen-rich cell periphery with mitochondria in the oxygen-poor core of the muscle fibre, thereby forming a continuous network. Thus, a membrane potential generated in the cell periphery can be dissipated over a large area and used to produce ATP in remote parts of the cell to fuel molecular motors during muscle contraction³. Moreover, mitochondrial fusion is markedly increased under stress conditions that involve mitochondrial ATP production⁹³ and during the G₁ to S transition, when mitochondrial ATP synthesis is enhanced⁹⁴. The appearance of highly interconnected fused mitochondrial networks in these cells is consistent with a role for mitochondrial fusion in the dissipation of energy. Hence, it seems that concerted activities of the mitochondrial fusion and fission machineries shape the mitochondrial compartment and adapt it to the specific requirements of the cells.

Mitochondrial quality control and ageing. Research over the past decades leaves no doubt that mitochondria have a crucial role in ageing. The mitochondrial theory of ageing postulates that the respiratory chain produces reactive oxygen species (ROS) as byproducts of oxidative phosphorylation. Because mitochondria are a major source for ROS, mtDNA is particularly vulnerable to ROS-induced mutations and lesions. As a result, gradual and progressive accumulation of mtDNA mutations leads to a loss of functional respiratory chain complexes, resulting in a decline of bioenergetic capacity and eventually age-associated pathologies and death⁹⁵. Mitochondrial dynamics was proposed to counteract this detrimental process through two activities: rescue of non-functional organelles by fusion and elimination of damaged organelles after fission.

Somatic mitochondrial mutations result in the coexistence of wild-type and mutant mtDNAs in the same cell, a state termed heteroplasmy. When two solitary mitochondria carry mutations in two different genes, both will have defects in respiration. However, when these mitochondria fuse, each fusion partner will contribute an intact allele and synthesize a functional gene product that is shared with the other

fusion partner, thereby restoring respiratory activity. In a proof-of-principle experiment, two respiration-deficient HeLa cell lines were established, each carrying a pathogenic mutation in a different mitochondrial tRNA gene. Remarkably, hybrids of these cell lines showed restoration of normal respiratory activity after a few days owing to mitochondrial fusion⁹⁶. Support for inter-mitochondrial complementation in the living organism was obtained from a mouse model that contained a mixture of intact and mutant mtDNAs. Irrespective of the level of heteroplasmy, mitochondria showed a homogenous pattern of respiratory activity at the cellular level as a result of fusion and intermixing of mitochondrial contents⁹⁷. These findings suggest that fusion of mitochondria and complementation of mitochondrial gene products are a defence mechanism against cellular ageing.

A recent study showed that mitochondrial fusion is important for the maintenance of a healthy mitochondrial population in muscle cells⁹⁸. Transgenic mice carrying specific disruptions in *Mfn1* and *Mfn2* in skeletal muscle display several hallmarks of muscular mitochondrial dysfunction, including loss of respiratory complex activity, mitochondrial swelling and compensatory proliferation, and muscle atrophy. These physiological abnormalities are preceded by severe loss of mtDNA and rapid accumulation of mtDNA mutations. Several factors were proposed to contribute to the decline of mitochondrial functions: inefficient mtDNA replication combined with inheritance defects, altered protein stoichiometries hampering maintenance and repair functions in solitary mitochondria, and lack of exchange of mitochondrial contents in heteroplasmic cells⁹⁸.

Autophagy is a process of self-degradation of cellular components that are harmful or no longer required. Damaged or surplus organelles or portions of cytosol are sequestered by double-membrane autophagosomes that fuse with lysosomes or vacuoles and are broken down by hydrolytic enzymes⁹⁹. The autophagic breakdown of mitochondria is termed mitophagy. It is tempting to speculate that mitophagy constitutes a mechanism to remove dysfunctional mitochondria from the cell and thereby prevent proliferation of mutated mtDNA. Support for this hypothesis came recently from a seminal study that described the behaviour of fluorescently labelled mitochondria in cultured mammalian cells¹⁰⁰. Mitochondrial division was found to frequently produce two uneven daughter organelles, one with high membrane potential and one with decreased membrane potential and reduced OPA1 levels. Intriguingly, mitochondria with decreased membrane potential and reduced OPA1 levels are less likely to be engaged in subsequent fusion events and, instead, are prone to removal by mitophagy. Remarkably, inhibition of fission decreases mitophagy and results in decline of respiratory capacity, whereas arrest of autophagy leads to the accumulation of mitochondria with low membrane potential and low OPA1. On the basis of these observations a hypothesis was proposed that integrates mitochondrial dynamics and turnover in the mitochondrial life cycle. Mitochondrial fission frequently generates solitary

Purkinje neuron

A large neuron in the cerebellar cortex with a single long axon and many branched dendritic extensions.

Reactive oxygen species

Reactive oxygen species (ROS) are chemically reactive molecules containing oxygen, such as superoxide anions, peroxides and hydroxyl radicals. Mitochondrial ROS are generated by incomplete reduction of molecular oxygen in the respiratory chain.

Table 2 | Human diseases associated with perturbations of mitochondrial dynamics

Molecular defect	Disease	Neuronal defect	Refs
Mutations in <i>OPA1</i> that impede mitochondrial fusion	Autosomal dominant optic atrophy	Degeneration of retinal ganglion cells and optic nerve	111,112
Mutations in <i>MFN2</i> that impede mitochondrial fusion	Charcot–Marie–Tooth disease type 2a	Degeneration of long peripheral sensory and motor neurons	113
Mutations in <i>DRP1</i> that impede mitochondrial fission	Unnamed	Abnormal brain development, optic atrophy and neonatal lethality	114
Mutations in <i>PINK1</i> or <i>PARK2</i> that disturb mitochondrial dynamics	Hereditary early onset Parkinson's disease	Degeneration of dopaminergic neurons in the substantia nigra	117–120

DRP1, dynamin-related protein 1; *MFN2*, mitofusin 2; *OPA1*, optic atrophy protein 1; *PARK2*, Parkin.

mitochondria that might either maintain an intact membrane potential and re-fuse with the mitochondrial network, or might be depolarized and depleted of *OPA1*, thereby preventing further rounds of fusion. This enables subsequent elimination by mitophagy¹⁰⁰. Therefore, mitochondrial division may contribute to a quality control mechanism that facilitates removal of damaged mitochondria from the cell.

Mitochondrial fission is important for apoptosis. A key event in apoptosis is mitochondrial outer membrane permeabilization, which releases cytochrome *c* and other pro-apoptotic factors from the intermembrane space into the cytosol to trigger downstream cell death pathways^{101,102}. Regulation of apoptosis involves *DRP1*-dependent mitochondrial fragmentation in a wide range of organisms, including yeast¹⁰³, worms¹⁰⁴, flies¹⁰⁵ and mammals¹⁰⁶. Furthermore, the observation that the pro-apoptotic proteins BAX and BCL-2 antagonist/killer (BAK) interact with *DRP1* and mitofusins points to an intense crosstalk of the machineries of mitochondrial dynamics and apoptosis^{81,107–109}. Although many issues remain controversial, it seems that mitochondrial fragmentation occurs early in the apoptotic pathway, just prior to or simultaneously with outer membrane permeabilization and before effector caspase activation. Further work is required to determine how the components of mitochondrial fission and fusion actively participate in programmed cell death.

Mitochondrial dynamics in human disease

Defects in mitochondrial fusion and fission primarily affect neuronal functions, as nerve cells have a high energy demand and strictly depend on mitochondrial functions, and neurons are particularly sensitive to perturbations of mitochondrial distribution¹¹⁰. Dysfunctions of mitochondrial dynamics are implicated in inherited and age-associated neurodegenerative diseases (TABLE 2).

Mutations in the mitochondrial fusion genes *OPA1* and *MFN2* cause degeneration of specific nerves. *OPA1* is the causative gene for autosomal dominant optic atrophy (ADOA), the most common form of inherited childhood blindness^{111,112}. Patients with ADOA experience progressive loss of vision owing to degeneration of retinal ganglion cells, the axons of which form the optic nerve. Mutations in *MFN2* cause Charcot–Marie–Tooth

disease type 2a¹¹³, which is characterized by progressive distal sensory and motor neuron impairments that result from degeneration of long peripheral nerves. Inherited diseases that are directly linked to essential fission components have not been described. However, a recent study reported the case of a newborn girl that carried a dominant-negative mutation in *DRP1*. The girl died 37 days after birth and exhibited, among other symptoms, severe neurological defects, including microencephaly, abnormal brain development and optic atrophy¹¹⁴.

Mitochondrial dynamics also have a role in the pathogenesis of age-associated progressive neurodegenerative disorders¹¹⁰, including Parkinson's disease. Loss-of-function mutations in *PINK1* and *PARK2* (which encodes Parkin) are the major cause of autosomal-recessive early-onset Parkinson's disease. *PINK1* is a protein kinase that is selectively stabilized in mitochondria with low membrane potential, where it recruits Parkin to mark impaired mitochondria and promote mitophagy^{115,116}. Studies in *D. melanogaster* have revealed many genetic interactions of *PINK1* and Parkin with fusion and fission components^{117,118}. Moreover, *D. melanogaster* mitofusin was identified as a target for ubiquitylation by Parkin¹¹⁹, suggesting that mitochondrial dynamics is an important factor in Parkinson's disease. However, loss of *PINK1* and Parkin has opposite effects on mitochondrial morphology in different systems. *PINK1* and Parkin promote mitochondrial fission in *D. melanogaster*^{117–119}, whereas they act as pro-fusion factors in human cells¹²⁰. Thus, it remains to be shown how *PINK1*, Parkin and mitochondrial dynamics can be integrated in mitochondrial quality control pathways in human cells.

Links between mitochondria and other organelles

Several recent studies revealed intriguing links between the machinery of mitochondrial dynamics and other organelles. Dnm1 and Fis1 in yeast, and *DRP1*, *FIS1* and *MFF* in mammalian cells, mediate the division of both mitochondria and peroxisomes^{56,121–123}. Moreover, *MAPL* was found in vesicles that bud off from the mitochondrial outer membrane and fuse with a subset of peroxisomes¹²⁴. It remains to be determined why mitochondria and peroxisomes share a division machinery and why they communicate by mitochondrion-derived vesicles. However, it is possible that these processes serve to

Cytochrome *c*

A small protein in the mitochondrial intermembrane space that transports electrons in the respiratory chain. It activates cell death pathways when released into the cytosol.

Caspase

An enzyme belonging to a family of proteases that execute cell death events late in the apoptotic pathway.

coordinate their activities in common biochemical pathways, such as β -oxidation of fatty acids or scavenging of peroxides.

It has been known for a long time from electron micrographs that mitochondria are often closely associated with the endoplasmic reticulum (ER). Surprisingly, one of the two mammalian mitofusin isoforms, MFN2, was found to form a tether between the ER and mitochondria. ER-located MFN2 is engaged in complexes with mitochondrial MFN1 or MFN2, thereby bridging the two organelles and bringing them close together to allow communication by Ca^{2+} signalling¹²⁵. The MFN2-dependent ER tether also has a role in the formation of autophagosomes. Mitochondria contribute membrane lipids to newly formed autophagosomes during starvation. As the mitochondrial mass remains constant during this process, the mitochondrion–ER tether is thought to ensure that mitochondrial lipids are immediately replenished from the ER. Consistent with this, loss of MFN2 markedly impairs starvation-induced autophagy¹²⁶. It therefore seems that mitochondrial behaviour is interwoven with many cellular pathways, so studies have to consider the possibility that other organelles may also be affected by changes in mitochondrial dynamics.

Perspectives

Research in the past 15 years led to the identification of the key proteins of mitochondrial fusion and fission in yeast and animals. In particular, comprehensive screens of yeast mutant collections have now systematically analysed almost 90% of the yeast genes for a role in mitochondrial distribution and morphology^{48,127}. Thus, we can be confident that most of the conserved core components are known. The next challenge is to mechanistically dissect these molecular machineries to learn how they achieve fusion and fission of a double membrane-bound organelle. Assembly and regulation of mitofusins and DRP1 are apparently much more complex in mammalian cells than in yeast. Future studies will yield further insights into the cellular pathways that adapt the shape of the mitochondrial compartment to the needs of differentiated cells. A picture emerges that the main function of mitochondrial dynamics is to ensure proper inheritance and distribution of mitochondria and to maintain them in a healthy state. We now have to determine the roles of the mediators of mitochondrial fusion and fission, and how dysfunctions contribute to disease mechanisms. Thus, the investigation of mitochondrial dynamics will remain an exciting field of research in the coming years.

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