Molecular Machinery of Mitochondrial Fusion and Fission

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Mitochondria generate energy by oxidative phosphorylation; play a crucial role in iron-sulfur cluster assembly; and participate in intermediary metabolism, calcium signaling, and apoptosis. They are bounded by a double membrane and contain ~800 (yeast) to 1500 (human) different proteins. Although the vast majority of mitochondrial proteins are encoded in the nucleus and post-translationally imported into the organelle, a handful of proteins required for respiration are encoded by the mitochondrial genome. In many eukaryotic cell types, mitochondria continuously move along cytoskeletal tracks and frequently fuse and divide (1). In recent years, it became clear that this dynamic behavior is important for many mitochondrial functions in cell life and death (2). Here, I will briefly summarize the cellular roles of mitochondrial dynamics and discuss the molecular machinery mediating mitochondrial membrane fusion and fission.

Cellular Roles of Mitochondrial Fusion and Fission

Mitochondrial morphology and copy number depend on the balance of fusion and fission activities. A shift toward fusion enables the cell to build extended interconnected mitochondrial networks, whereas a shift toward fission generates numerous morphologically and functionally distinct small spherical organelles. This adaptation of the mitochondrial compartment to cellular demands is critical for a number of important processes (Fig. 1). Large mitochondrial networks are frequently found in metabolically active cells. They consist of extended and interconnected mitochondrial filaments and act as electrically united systems. These networks enable the transmission of mitochondrial membrane potential from oxygen–rich to oxygen–poor areas and thereby allow an efficient dissipation of energy in the cell (3). Furthermore, the connectivity of the mitochondrial network is an important factor that determines the cell’s response to calcium signals (4), and fusion of mitochondria is an essential step in certain developmental processes such as embryonic development (5) and spermatogenesis (6).

In addition to its role in network formation, fusion serves to mix and unify the mitochondrial compartment, an activity that is thought to constitute a defense mechanism against aging. It is estimated that 1–5% of the oxygen consumed during oxidative phosphorylation is converted to ROS as an unavoidable by-product of respiratory chain function. As mtDNA is directly located at the site of ROS production, it is particularly vulnerable to ROS-mediated mutations. These mutations accumulate with age until a bioenergetic threshold is breached, resulting in mitochondrial dysfunction. The mitochondrial theory of aging predicts that an accumulation of mtDNA mutations eventually leads to age-associated pathologies and death (7). Fusion of mitochondria counteracts the manifestation of respiratory deficiencies because it allows complementation of mtDNA gene products in heteroplasmic cells that have accumulated different somatic mutations (8).

Similar to fusion, mitochondrial fission also plays a key role in cell life and death. As mitochondria are propagated by growth and division of pre-existing organelles, mitochondrial inheritance depends on mitochondrial fission during cytokinesis (9). Furthermore, mitochondrial division is important for several developmental and cell differentiation processes, including embryonic development in Caenorhabditis elegans (10) and formation of synapses and dendritic spines in neurons (11). Last but not least, the mitochondrial fission machinery actively participates in the programmed cell death pathway (apoptosis) by inducing fragmentation of the mitochondrial network prior to cytochrome c release and caspase activation (12).

Molecular Machinery of Mitochondrial Fusion

The major components of the mitochondrial fusion and fission machineries have been evolutionarily conserved from yeast to man (Table 1). Due to this conservation and the availability of sophisticated genetic, cytological, and biochemical assays, bakers’ yeast (Saccharomyces cerevisiae) emerged as one of the prime model organisms to study the molecular mechanisms of mitochondrial membrane fusion and fission (13–15).

The core machinery mediating fusion in yeast consists of three proteins: Fzo1 and Ugo1 in the outer membrane and Mgm1, an intermembrane space protein anchored to the inner membrane (Fig. 2). Yeast cells lacking one of these components contain fragmented mitochondria and have defects in mtDNA inheritance. Exchange of mitochondrial matrix content is blocked both in vivo and in vitro, indicating that a block of fusion is the primary defect in Δfzo1, Δugo1, and Δmgm1 deletion mutants (16–21).

Fzo1 is a large GTPase that assembles into a high molecular mass complex in the outer membrane. It has two transmembrane regions, with the major parts of the protein extending into the cytosol and a short loop exposed to the intermembrane space. The large N-terminal part consists of a GTPase domain flanked by two predicted coiled coils. The smaller C-terminal part contains another coiled-coil region (16, 17, 22). Fzo1-related proteins have been conserved throughout the fungal and animal kingdoms. Drosophila FZO, the founding member of the protein family, plays a highly specialized role in spermatogenesis (6), whereas a related protein, DMFN, is widely expressed in male and female flies (23). Mammalian cells contain two ubiquitously expressed homologs termed mitofusins (MFN1 and MFN2). Metazoan mitofusins share the same

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2 The abbreviations used are: ROS, reactive oxygen species; CMT, Charcot-Marie-Tooth disease.
topology and domain organization with yeast Fzo1, with the exception that they lack the most N-terminal coiled-coil region (24). Ugo1 is a yeast mitochondrial outer membrane protein that contains up to five transmembrane regions (20, 25). Homologs of Ugo1 in higher organisms are unknown.

Mgm1, a dynamin-related GTPase in the intermembrane space, contains a cleavable N-terminal presequence for import, a hydrophobic transmembrane anchor, a GTPase domain, a middle domain, and a GTPase effector domain (13, 21). Mgm1 is present in two isoforms: a large form anchored in the inner membrane and a small form lacking the hydrophobic membrane anchor. The small form is generated by alternative processing by the rhomboid-related inner membrane protease, Pcp1 (26, 27). OPA1, the mammalian homolog of Mgm1, is present in even greater variety because eight tissue-specific splice variants exist in addition to the large and small isoforms (28).

As double membrane-bounded organelles, mitochondria face the topological problem that they have to fuse four membranes in a coordinated manner. How is this achieved? The first step in cellular membrane fusion events is the formation of trans complexes involving proteins on the surface of both fusion partners. This docking step ensures specificity of the fusion reaction and mediates apposition of adjacent membranes. Several lines of evidence indicate that Fzo1/mitofusins play a key role in formation of the trans complex. First, wild-type mitochondria fail to fuse with mitochondria lacking Fzo1/mitofusins (19, 29); second, a mitofusin docking complex formed on distinct apposing membranes has been identified by immunoprecipitation (30); and third, the C-terminal heptad repeat regions of MFN1 form a dimeric antiparallel coiled coil that is ideally suited to tether the membranes of adjacent mitochondria together (29).

The second step in membrane fusion is lipid bilayer mixing. The capability to form α-helical rods by pairing of coiled-coil domains is a hallmark of membrane fusion machineries such as SNAREs (soluble N-ethylmaleimide-sensitive factor attachment protein receptors) and viral fusion proteins. Formation of these rods draws apposing membranes close together and thereby initiates lipid bilayer mixing (31). Intriguingly, Fzo1/mitofusins possess all domains that can be predicted to be present in a fusogen: they have several coiled-coil regions, two transmembrane domains, and a GTPase domain, which could provide energy to overcome the energy barrier of lipid bilayer mixing. Although it has not been demonstrated yet whether their activity is sufficient to act as fusogens for the outer membrane, it is clear that Fzo1/mitofusins play a central role in this process (13, 15, 32).

After completion of outer membrane fusion, merging of the mitochondrial inner membranes must be initiated. Assays monitoring mitochondrial content mixing in vivo and in vitro revealed that fusion of the inner membrane is particularly sensitive to dissipation of the electrical membrane potential and functionally separable from fusion of the outer membrane; these findings indicate that a distinct fusion machinery is present in the inner membrane (19, 33). Mechanistic analysis of conditional mutants recently assigned a key role to Mgm1 as a mediator of inner membrane fusion. Similar to Fzo1 in the outer membrane, Mgm1 has the capability to form trans complexes that tether apposing inner membranes. Interestingly, fusion is blocked also in mitochondria of mgm1 mutant strains that show defects in a stage after inner membrane tethering. This suggests that Mgm1 and its mammalian homolog, OPA1, play a key role in inner membrane lipid mixing (15, 18).

Coordinated activity of the machineries in the outer and inner membranes must ensure the fidelity of double membrane fusion. Intriguingly, Fzo1 is found in contact sites connecting the mitochondrial outer and inner membranes, and mutants that cannot establish contacts of Fzo1 with the inner membrane show defects in mitochondrial fusion in vivo (17, 22). These findings suggest that physical contacts of the outer membrane fusion machinery with the inner membrane are required to coordinate double membrane fusion. As Ugo1 has been found in a complex with Fzo1 and Mgm1 (21, 34), it is likely that Ugo1 plays an important role in coordinating outer and inner membrane fusion events in yeast.

**Molecular Machinery of Mitochondrial Fission**

The core machinery of mitochondrial fission in yeast consists of four proteins: Fis1 in the outer membrane and three cytosolic proteins (Dnm1, Mdv1, and Caf4) that assemble at sites of mitochondrial division on the organelar surface (Fig. 3). Yeast cells defective in outer membrane fusion contain elaborate, extensively interconnected mitochondrial nets due to ongoing fusion unopposed by fission (35–39).

Yeast Dnm1 is a dynamin-related protein containing an N-terminal GTPase domain, a middle domain, an insert B of unknown function, and a C-terminal GTPase effector domain. Cytosolic Dnm1 assembles into punctate structures on mitochondria in a dynamic manner (40). Homologous dynamin-related proteins have been shown to play a role in mitochondrial fission in mammals (DRP1, also termed DLP1), worms (DRP-1), and higher plants (ADL1 and ADL2) (13).

Fis1 is a tail-anchored outer membrane protein that is evenly distributed on the mitochondrial surface (38). Its N-terminal cytosolic domain forms a six-helix bundle containing tandem tetratricopeptide repeat motifs. This domain provides two interaction interfaces for the recruitment of fission factors from the cytosol (41). Fis1-related proteins (termed hFis1 in humans)
TABLE 1
Core components of the mitochondrial fusion and fission machineries
OM, outer membrane; IM, inner membrane; IMS, intermembrane space.

| Process/yeast | Orthologs in higher eukaryotes | Location | Proposed function |
|---------------|-------------------------------|----------|------------------|
| **Fusion**    |                               |          |                  |
| Fzo1          | MFN1 and MFN2 (mammals), FZO and DMFN (D. melanogaster) | OM, OM fusion |                  |
| Ugo1          |                               | OM       | Coordination of OM and IM fusion |
| Mgm1          | OPA1 (mammals)                | IM and IMS | IM fusion        |
| **Fission**   |                               |          |                  |
| Dnm1          | DRP1/DLP1 (mammals), DRP-1 (C. elegans), ADL1 and ADL2 (A. thaliana) | Cytosol and OM, OM | OM fission, Receptor for OM fission machinery |
| Fis1          | hFis1 (humans)                | OM       | Adaptor between Fis1 and Dnm1 |
| Mdv1          |                               | Cytosol and OM | Redundant with Mdv1 |
| Caf4          |                               |          |                  |

FIGURE 2. Model of the molecular machinery of mitochondrial fusion in yeast. Two Fzo1 molecules are shown tethering adjacent mitochondria by assembling a dimeric antiparallel coiled coil (cc) of their C-terminal heptad repeat regions (29). It should be noted that Fzo1 in mitochondria is part of a large 800-kDa complex of unknown composition (16). Ugo1 contains up to five membrane-spanning regions, as depicted here; however, alternative topologies with fewer transmembrane regions have also been proposed (25). It is unknown which parts of Ugo1 interact with Fzo1 and Mgm1. Mgm1 exists in two forms in mitochondria: a long form containing a transmembrane region in the inner membrane (IM) and a shorter form lacking this region due to cleavage by Pcp1 (26, 27). It is unknown which domains of Mgm1 interact with the outer membrane (OM) components. The N-terminal end of each polypeptide is indicated. GED, GTPase effector domain; IMS, intermembrane space; MD, middle domain.

have been evolutionarily highly conserved in fungi and animals (42).

Mdv1 and Caf4 are two related soluble proteins that perform redundant functions in mitochondrial fission and share the same domain organization (37, 39). An N-terminal extension contains two α-helices that interact with Fis1; a coiled-coil domain is thought to mediate homo-oligomeric interactions; and a C-terminal WD40 repeat region is predicted to form a seven-bladed propeller that binds to Dnm1 (41, 43). Structural or functional homologs of Mdv1 and Caf4 in multicellular eukaryotes are not known.

Current models of mitochondrial division leave no doubt that Dnm1 is the key player mediating membrane scission (13–15). Fis1 functions as a membrane receptor, and Mdv1 and Caf4 serve as adaptor proteins to recruit Dnm1 to the sites of mitochondrial fission. In a first step of the division reaction, Fis1 and Mdv1/Caf4 aid the dynamic assembly of Dnm1 on the mitochondrial surface. As it has been shown that Dnm1 self-assembles into curved filaments or extended spirals in vitro (44), it seems likely that Dnm1 on mitochondria assembles into spirals surrounding the organelle completely. As the curvature of Dnm1 filaments depends on the nucleotide bound, GTP hydrolysis might ultimately drive constriction and scission of the mitochondrial membranes (13, 15, 44). In this scenario, the function of Dnm1 would be very similar to that of other dynamin family members that act in numerous intracellular membrane scission events (45).

Much less is known about fission of the inner membrane. It is conceivable that the activity of Dnm1 is sufficient to sever both mitochondrial membranes simultaneously. However, circumstantial evidence points to the existence of a separate division machinery in the inner membrane. The diameter of a tubular mitochondrion is ~300–400 nm, whereas the diameter of Dnm1 spirals is only ~100 nm (44). Thus, the diameter of the mitochondrion must be significantly reduced at the site of divi-
sion to allow formation of Dnm1 spirals. Consistently, it has been observed that Dnm1 assembly on mitochondria produces a successful division of the organelle only when it coincides with a prior constriction event (40). It is conceivable that constriction is a result of inner membrane division at this site. In fact, analysis of ∆dmn1 deletion mutants in yeast and dominant-negative drp-1 mutants in C. elegans indicated that inner membrane division can cause separation of matrix compartments in the absence of outer membrane division (10, 46).

Two components have been proposed to contribute to inner membrane division: Mdm33 in yeast and MTP18 in mammals. Mdm33 is a mitochondrial inner membrane protein exposing extensive coiled-coil domains in the matrix. Overexpression of Mdm33 induces septation and vesiculation of the inner membrane possibly due to enhanced inner membrane fission activity, whereas mutants lacking Mdm33 contain giant ring-shaped mitochondria (47). MTP18 is an unrelated protein in the inner membrane of mammalian mitochondria. Overexpression of MTP18 induces fragmentation of the mitochondrial network, whereas depletion results in formation of highly fused mitochondria (48). Based on these observations, a role in inner membrane fission has been proposed. However, due to the lack of functional assays, it is presently difficult to prove a direct role of Mdm33 and MTP18 in inner membrane division.

Regulation of Mitochondrial Fusion and Fission

An intricate balance of fusion and fission is required to maintain mitochondrial morphology in steady state. In response to intra- or extracellular signals, a shift toward fusion or fission allows the cell to reorganize the mitochondrial network and adapt its morphology to the cellular demands. The importance of keeping the right balance is evident from the fact that defects in mitochondrial dynamics lead to a variety of diseases (Fig. 1). For example, OPA1 is the causative gene for type 1 autosomal dominant optic atrophy, a common form of inherited childhood blindness (28), and mutations in the MFN2 gene lead to CMT type 2A, a neurodegenerative disorder clinically characterized by the gradual degeneration of peripheral neurons (49). Similarly, defects in mitochondrial division have been proposed to be associated with CMT type 4A, a recessive disease involving myelin or axonal defects (50).

Given the functional importance of mitochondrial shape, distribution, and connectivity, it is clear that the rates of fusion and fission must be tightly controlled. Although the machineries of fusion and fission have been highly conserved, the mechanisms to control their activities are much more diverse. A few examples will illustrate the diversity of regulatory pathways that have evolved in different eukaryotic cell types.

Their central role as core components of the fusion machinery makes Fzo1/mitofusins prime targets for regulatory machineries acting on their expression, assembly, or degradation. For example, the male-specific FZO protein in Drosophila exerts a highly specialized role in spermatogenesis and is expressed only in spermatids during a specific developmental stage (6). Two mammalian pro-apoptotic Bcl-2 family members, Bax and Bak, induce mitochondrial fusion by regulating the assembly and submitochondrial distribution of MFN2. Intriguingly, their activity is required both in apoptosis and in healthy cells, pointing to an intimate connection of mitochondrial remodeling and programmed cell death (51). Even in a relatively simple cell such as yeast, two pathways controlling Fzo1 turnover have been described: the F-box protein Mdm30 governs degradation of Fzo1 by a proteasome-independent mechanism in vegetatively growing cells (52), whereas turnover of Fzo1 is proteasome-dependent and does not involve Mdm30 in cell cycle-arrested cells (53).

DRP1, the key component of mitochondrial division in mammalian cells, is subject to similarly complex regulatory mechanisms. It interacts with MARCH-V (also termed MITOL), an F-box protein of the outer membrane that controls mitochondrial fission by virtue of its ubiquitin ligase activity (54, 55). The stability of DRP1 is further controlled by modification with the small ubiquitin-like modifier SUMO (56), and phosphorylation of DRP1 by cyclin-dependent kinases induces fragmentation of mitochondria during mitosis (57).

Although several additional pathways regulating mitochondrial dynamics have been described recently (58), the examples mentioned above suffice to underscore the importance of the coordination of mitochondrial fusion and fission with the developmental and metabolic needs of eukaryotic cells. It is safe to predict that the coming years will reveal many new components and mechanisms contributing to the dynamic behavior of mitochondria in cell life and death.

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