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Review

Bioenergetic role of mitochondrial fusion and fission ☆

Benedikt Westermann *

Zellbiologie, Universität Bayreuth, 95440 Bayreuth, Germany

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ABSTRACT

Mitochondria are highly dynamic organelles. Frequent cycles of fusion and fission adapt the morphology of the mitochondrial compartment to the metabolic needs of the cell. Mitochondrial fusion is particularly important in respiratory active cells. It allows the spreading of metabolites, enzymes, and mitochondrial gene products throughout the entire mitochondrial compartment. This serves to optimize mitochondrial function and counteracts the accumulation of mitochondrial mutations during aging. Fragmented mitochondria are frequently found in resting cells, and mitochondrial fission plays an important role in the removal of damaged organelles by autophagy. Thus, mitochondrial fusion and fission both contribute to maintenance of mitochondrial function and optimize bioenergetic capacity. Multiple signalling pathways regulate the machinery of mitochondrial dynamics to adapt the shape of the mitochondrial compartment to the metabolic conditions of the cell. This article is part of a Special Issue entitled: 17th European Bioenergetics Conference (EBEC 2012).

1. Introduction

Mitochondrial morphology is highly varied in different cell types. The name *mitochondrion*, coined by Benda in 1898, is derived from the Greek words *mitos* (meaning thread) and *chondros* (meaning grain) [1]. It describes the appearance of mitochondria as threads of granules in spermatocytes. Nowadays, live cell imaging and electron microscopy allow the analysis of mitochondrial morphology, distribution, and behavior at high spatial and temporal resolution in a great variety of organisms and tissues [2,3]. Depending on the cell type and physiological conditions, mitochondria can be present either as numerous morphologically distinct small organelles, or they can form large interconnected networks [4–6]. The interconnectivity and dynamics of the mitochondrial compartment are determined by mitochondrial fusion and fission. Mitochondrial dynamics serves a variety of different functions, including mitochondrial distribution and inheritance [7,8], remodelling of mitochondria during developmental processes [9,10], and coordination of cell death programs by release of pro-apoptotic factors from the intermembrane space [11,12].

The core machinery of mitochondrial dynamics consists of three large GTPases that fuse and divide the mitochondrial membranes (Table 1). As this machinery has been highly conserved during evolution, it can be studied in yeast and mammals. Mitofusins (Fzo1 in yeast, Mfn1 and Mfn2 in mammals) are large GTPases that are crucial for outer membrane fusion [13–15]. Mgm1 in yeast and Opa1 in mammals are dynamin-related proteins of the intermembrane space required for inner membrane fusion [16,17], and Dnm1 in yeast and Drp1 in mammals are dynamin-related proteins that assemble on the mitochondrial surface to mediate mitochondrial fission [18,19]. The cellular roles of mitochondrial dynamics and the assembly, function, and regulation of the molecular machinery of mitochondrial fusion and fission have been discussed in several recent reviews [20–24]. Here, I will elaborate on the adaptation of mitochondrial morphology to the bioenergetic requirements of the cell and focus on the roles of mitochondrial fusion and fission in this process. It should be noted that extensive adaptations of mitochondria to bioenergetic conditions also occur at the level of inner membrane ultrastructure and remodelling of mitochondrial cristae. These processes have been discussed recently in a comprehensive manner [6,25–27].

2. Relation of mitochondrial distribution and dynamics to cellular energy requirements

Mitochondria are often positioned at intracellular sites of high energy demand. The arrangement of mitochondria in mammalian sperm cells impressively illustrates this fact. Mitochondria are located at the proximal part of the flagellum in a region called the midpiece where they form helical structures that are wrapped around the axoneme [28,29]. They are thus ideally positioned to supply the flagellar motor proteins with ATP to fuel the vigorous movements of the sperm cell. Remarkably, it was shown that the size of mitochondria even reflects sexual behavior, as sperm cells of primate species with promiscuous behavior have a larger midpiece than sperm cells of

Abbreviations: mtDNA, mitochondrial DNA; ROS, reactive oxygen species

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* Tel.: +49 921 554300; fax: +49 921 554301.
E-mail address: benedikt.westermann@uni-bayreuth.de.

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Table 1
The core machinery of mitochondrial fusion and fission.

	Yeast	Mammals
Outer membrane fusion	Fzo1	Mfn1, Mfn2
Inner membrane fusion	Mgm1	Opa1
Fission	Dnm1	Drp1

monogamous species. Apparently, a large mitochondrial volume in the midpiece – and thus a high bioenergetic capacity – confers an advantage in sperm competition when the females mate with multiple partners [30]. Likewise, the high energy demand of muscle cells requires an intracellular positioning of mitochondria close to the motor proteins that consume ATP during muscle contraction. Mitochondria are embedded between the myofibrils along their entire length to provide uniform supply of ATP to the sarcomeres [31–33]. The highly regular arrangement of mitochondria is particularly impressive in striated muscle cells of insect flight muscles [34]. Moreover, mitochondria were found to accumulate at sites of high energy demand in neurons [35] and migrating lymphocytes [36]. While these examples demonstrate an adaptation of mitochondrial distribution and morphology to the bioenergetic requirements in highly differentiated cells, the dynamic remodelling processes of the mitochondrial compartment were most extensively studied in yeast and mammalian tissue culture cells.

Baker's yeast, *Saccharomyces cerevisiae*, is a valuable model system to study mitochondrial dynamics since it is easy to cultivate, amenable to genetic manipulations, and able to switch between respiratory and fermentative metabolism [37]. Fermentable carbon sources, such as glucose or fructose, are the preferred substrates of yeast. Even when oxygen is available, most ATP is generated by glycolysis with ethanol as an end product of fermentation, and respiratory functions are largely repressed under these conditions. Only when fermentable carbon sources are exhausted, genes required for respiration are induced, and ATP is produced by metabolism of non-fermentable carbon sources and mitochondrial respiration [38]. Shape, size, and number of mitochondria are adapted to the growth conditions. Yeast cells contain only few mitochondria when they are grown under anaerobic conditions, whereas mitochondrial mass and number are markedly increased under aerobic growth [39,40]. Logarithmically growing yeast cells contain an interconnected mitochondrial network below the cell cortex which becomes much larger and more elaborate after a shift from fermentable to non-fermentable carbon sources [39,41,42]. On the other hand, transfer of cells from respiratory to fermentative conditions leads to a simplification of the mitochondrial network within a few hours [43]. The mitochondrial network of metabolically active, logarithmically growing cells is highly dynamic with up to 2.5 fusion and fission events per minute and cell [43]. Its position at the cell periphery places the mitochondria near the point of entry of oxygen, and the elongated shape of mitochondrial tubules may be advantageous for energy dissipation in the cell [44]. The mitochondrial network fragments and forms many small, round mitochondria upon entry into stationary phase [39,45,46]. Taken together, these studies suggest that an elaborated, dynamic, and interconnected mitochondrial network best meets the needs of respiratory active yeast cells.

As it is difficult to study mitochondrial behavior in mammalian tissues in vivo, most studies addressing mitochondrial dynamics in mammals were performed with cultured cells. However, in contrast to aerobic tissues that produce most ATP by mitochondrial respiration, many cultured cell lines were found to produce ATP mainly by glycolysis. Thus, observations made with cultured cells should be interpreted with caution, as each primary or immortal cell line may exhibit unique properties, and the bioenergetic state and mitochondrial morphology and dynamics may strongly depend on culture conditions [47]. Keeping these caveats in mind, it is not surprising that a broad range of different mitochondrial morphologies were found in cultured mammalian cells, even in the same cell lines. At the one end of the spectrum are morphologically distinct small mitochondrial grains and threads that were observed for example in HeLa cells, COS-7 cells, cortical astrocytes and neurons, HUVEC, and hepatocytes [48]. At the other extreme are long, interconnected mitochondrial filaments that were found in human fibroblasts [49], dynamic and electrically coupled mitochondria in COS-7 cells [50], and branched mitochondrial networks in HeLa cells [51]. Several studies showed that inhibition of respiratory chain complexes by drug treatment induces fragmentation of the mitochondrial network. This was observed, for example, in HeLa cells [52,53], CV1-4A cells [52,54], mouse embryonic fibroblasts [54], human skin fibroblasts [55], cultured cortical neurons [55,56], MRC5 fibroblasts [57], and other cell types [47]. In contrast, some cell types retain filamentous mitochondria during respiratory chain inhibition, and the phenotypes of respiratory-deficient cells lacking an intact mitochondrial genome are ambiguous [47]. Mitochondria appear more elaborately interconnected and ramified in HeLa cells when mitochondrial respiration is induced by growth in galactose-containing medium (in comparison to glucose medium) [58]. However, this effect was not observed in MRC5 fibroblasts [58]. In sum, the majority of the available data point to a functional link between changes of energy metabolism and adaptations of mitochondrial morphology in mammalian cells. It appears that interconnected mitochondrial networks are frequently present in metabolically and respiratory active cells, whereas small and fragmented mitochondria are more prevalent in quiescent and respiratory inactive cells.

3. Bioenergetic role of mitochondrial fusion

Mitochondrial fusion allows efficient mixing of mitochondrial content, and it generates extended mitochondrial networks. Both effects are advantageous under conditions of high energy demand, and disruption of mitochondrial fusion results in mitochondrial dysfunction and loss of respiratory capacity both in yeast and in mammalian cells [13,15,59,60].

Deletion of the *FZO1* or *MGM1* genes, encoding key components of the mitochondrial fusion machinery, leads to rapid loss of the mitochondrial genome in yeast [13,15,61,62]. As several respiratory chain subunits are encoded by the mitochondrial DNA (mtDNA), it is difficult to determine whether loss of fusion directly contributes to a decline of respiratory capacity, or whether respiratory defects in fusion-deficient yeast mutants are an indirect consequence of a defect in mtDNA inheritance. Deletion of the *DNM1* gene, encoding a key mediator of mitochondrial fission, extends life span in yeast [63]. It is not exactly known whether longevity is directly related to the highly fused, interconnected mitochondrial network characteristic for fission-defective yeast mutants, or whether it is linked to the inactivation of cell death pathways or other reasons. Furthermore, deletion of the *MGM1* gene reduces life span in yeast [64], suggesting that mitochondrial fusion is beneficial for cell physiology. However, it remains unknown whether loss of mtDNA in *mgm1* mutants [61] has an impact on life span, and whether there is a direct link between mitochondrial fusion activity and respiratory capacity in yeast.

Mouse embryonic fibroblasts lacking the fusion components Mfn1 or Mfn2 are able to maintain mtDNA, but show a stochastic loss of membrane potential in a subset of mitochondria [60]. Strikingly, mutant or RNAi-treated cells that contain highly fragmented mitochondria, but retain residual mitochondrial fusion activity, escape major cellular dysfunction. In contrast, cells that lack any detectable fusion activity suffer reduced respiratory capacity [59]. Thus, mitochondrial fusion and intermixing of mitochondrial content, rather than maintenance of the tubular mitochondrial shape, appear to be a major factor in maintenance of respiratory capacity in mammalian cells. The reason is not exactly known. However, it is conceivable that fragmentation of the mitochondrial network inevitably generates a subfraction

of mitochondria that are devoid of mtDNA (or other essential components of the respiratory system) [8]. In the absence of any fusion activity these mitochondrial fragments will be depleted of mtDNA-encoded respiratory chain subunits and will be unable to participate in ATP synthesis. An integration of these organelles into the mitochondrial network by fusion will enable them to contribute to respiratory activity and increase the bioenergetic capacity of the cell.

Content mixing and complementation of gene products in fused mitochondria were proposed to be crucial for maintenance of mitochondrial functions and counteract cellular aging. The mitochondrial theory of aging postulates that reactive oxygen species (ROS) are generated as unavoidable byproducts of respiration, and that ROS induce mutations and lesions in mtDNA. The progressive age-associated accumulation of mitochondrial mutations then results in compromised mitochondrial functions, loss of bioenergetic capacity, and eventually pathologies and death [65,66]. During the process of aging, different mutations accumulate in different mtDNA molecules. Thus, wild-type mtDNA coexists with different mutant alleles or deletions, a state termed heteroplasmy. When individual mitochondria have acquired mutations in different genes, each mitochondrion will be respiratory deficient. However, when these mitochondria fuse, each fusion partner contributes an intact allele, and complementation of gene products restores respiratory activity [67]. Support for inter-mitochondrial complementation in heteroplasmic cells was obtained from cell and mouse models. In a proof-of-principle experiment, two respiratory-deficient HeLa cell lines were established that carry pathogenic mutations in different mitochondrial tRNA genes. Strikingly, hybrids of these cell lines show restoration of respiration after a few days owing to mitochondrial fusion [68]. Similarly, respiratory activity is maintained by mitochondrial fusion in a mouse model that contains a mixture of wild-type and mutant mtDNAs [69]. These findings suggest that mitochondrial fusion contributes to maintenance of mitochondrial functions in heteroplasmic cells and thereby constitutes a defence mechanism against aging.

In some cell types mitochondrial fusion generates large, extended networks that constitute electrically coupled systems [49,50]. These systems were proposed to operate as intracellular power-transmitting cables [70]. According to this hypothesis, respiratory chain complexes generate a membrane potential in oxygen-rich areas of the cell, and this membrane potential is then transmitted along mitochondrial filaments to remote areas of the cell where it can be used by the ATP synthase to generate metabolic energy in oxygen-poor parts of the cell. It is conceivable that efficient dissipation of membrane potential is especially important in large cells that have a particularly high energy demand, such as muscle cells [70].

Several recent reports underscore the importance of mitochondrial fusion under conditions of high energy demand in mammals. It was shown that some cell stressors, including UV irradiation and several drugs that inhibit cytosolic protein synthesis, can trigger increased mitochondrial fusion in mouse embryonic fibroblasts, a process termed stress-induced mitochondrial hyperfusion. Mitochondria elongate and form a mesh of highly interconnected filaments in an Mfn1 and Opa1-dependent manner. Stress-induced mitochondrial hyperfusion is accompanied by increased mitochondrial ATP production. It is conceivable that fusion is necessary to optimize mitochondrial function in order to allow the cell to cope with increased energy demand during selective forms of stress [71]. A mouse model for neurodegeneration caused by loss of mitochondrial fusion was established by targeted removal of Mfn2 from the cerebellum. Purkinje cells of these mice suffer aberrant mitochondrial distribution, ultrastructure, and respiratory chain activity [8]. Likewise, conditional deletion of Mfn1 and Mfn2 in differentiated skeletal muscle causes severe mitochondrial dysfunction, compensatory mitochondrial proliferation, and muscle atrophy. These defects are accompanied by the accumulation of point mutations and deletions in the mitochondrial genome and depletion of mtDNA [72]. These observations impressively illustrate the importance of mitochondrial fusion for maintenance of respiratory capacity in tissues that have a high metabolic activity.

The bioenergetic state of the cell may become critical upon starvation. Autophagy, a process of self-degradation of cellular components, plays an important role in the cellular response to nutrient deprivation. Organelles and cytosolic constituents are engulfed by a phagophore (also called isolation membrane) in a non-selective manner, and an autophagosome is formed that fuses with the lysosome and delivers its contents to degradation [73,74]. Two recent studies showed that the activity of the mitochondrial fission protein Drp1 is inhibited during starvation. This leads to elongation of mitochondria, as fusion is no longer opposed by fission. Intriguingly, elongated mitochondria are spared from engulfment by the phagophore and subsequent degradation. It is conceivable that this mechanism permits mitochondria to maximize cellular energy production and sustain cell viability during nutrient deprivation [75,76].

4. Bioenergetic role of mitochondrial fission

Mitochondrial division serves a variety of different functions. These include partitioning and inheritance of the organelles during cell division, release of cytochrome c and other intermembrane space proteins during apoptosis, and generation of transportable mitochondrial units for movement along the cytoskeleton [20,22,24]. While these functions are not directly related to bioenergetics, it was proposed that mitochondrial fission also serves to eliminate damaged organelles from the mitochondrial network in order to allow their removal by autophagy. This activity supposedly constitutes an organellar quality control mechanism and contributes to maintenance of bioenergetic capacity [77].

The observation of fluorescently labelled mitochondria in cultured mammalian cells revealed that mitochondrial division frequently generates two uneven daughter organelles, one with high membrane potential and another one with decreased membrane potential. Strikingly, mitochondria with low membrane potential were found to have reduced levels of the inner membrane fusion factor Opa1, and thus are less likely to re-fuse with the mitochondrial network. Instead, these dysfunctional mitochondria are removed from the cell by autophagy [78]. Thus, mitochondrial fission followed by selective fusion provides a mechanism to segregate damaged and dysfunctional mitochondria and permit their degradation by autophagy. In the long term, this mechanism contributes to the maintenance of a healthy mitochondrial population and maintenance of bioenergetic capacity [78].

It is unknown whether mitochondrial division contributes to organellar quality control in a similar way in yeast. It was shown that *atp6* mutants with compromised ATP synthase activity show a shift of expression of Mgm1 isoforms, leading to reduced fusion activity and mitochondrial fragmentation [79]. While it is conceivable that adjustment of Mgm1 activity could provide a means to adapt mitochondrial morphology to the energetic state of the cell [79], a recent study showed that the fission protein Dnm1 and its cofactors are not required for degradation of mitochondria by the autophagic machinery in yeast [80].

5. Adaptation of mitochondrial dynamics to bioenergetic conditions

What are the molecular processes that adapt the activities of the mitochondrial fusion and fission machineries to the bioenergetic state of the cell? At least three different, mutually non-exclusive mechanisms likely play important roles: first, the activity of the mitochondrial fusion machinery might directly respond to the bioenergetic state of mitochondria; second, several cellular signalling pathways modulate the activity of fusion and fission proteins; and third, the expression of key factors of mitochondrial dynamics is regulated at

the transcriptional level. We are just beginning to understand the complex regulation of mitochondrial dynamics, and different mechanisms and pathways prevail in different organisms and cell types. While more comprehensive discussions of these regulatory mechanisms can be found in several recent reviews [20,23,24,81–84], I will highlight here just a few examples to illustrate the response of mitochondrial dynamics to changes of the bioenergetic conditions of the cell.

Many respiratory-deficient yeast mutants have a wild type-like mitochondrial morphology [85], suggesting that the mitochondrial fusion machinery is able to maintain at least some activity when the mitochondrial membrane potential is reduced. Likewise, mitochondrial fusion activity in mammalian cells can be observed in the absence of a functional respiratory chain or after significant reduction of cellular ATP levels [53]. However, dissipation of the electrical gradient across the inner membrane with ionophores completely eliminates fusion of yeast mitochondria in vitro [86], and mitochondrial fusion in mammalian cells is strongly inhibited by treatment with protonophores that dissipate the mitochondrial membrane potential [53,87]. Thus, mitochondrial fusion requires a potential across the inner membrane. As the levels of Mgm1 isoforms in yeast and its homolog Opa1 in mammals were shown to be dependent on the bioenergetic state of mitochondria [78,79], it is conceivable that these proteins play a key role in adaptation of mitochondrial fusion activity in response to changes of the mitochondrial membrane potential.

Numerous cellular signalling pathways were shown to regulate mitochondrial dynamics in yeast and mammals. These signalling pathways mediate ubiquitylation, sumoylation, phosphorylation, nitrosylation, or proteolytic processing of key components of the mitochondrial fusion and fission machineries in response to cell cycle progression, pathogenic conditions, induction of cell death, or exogenous challenges (reviewed in Refs. [20,23,24,81–84,88]). The following example may suffice to illustrate the importance of post-translational modifications for the adaptation of mitochondrial dynamics to the bioenergetic state of the cell. cAMP-dependent protein kinase (PKA) is a central regulator of cellular respiration [84], and Drp1 was identified as a target of PKA, which inhibits mitochondrial fission through phosphorylation of Drp1 at a conserved serine residue [89,90]. It was shown recently that mitochondrial elongation during starvation depends on phosphorylation of Drp1 by PKA [76], and that mitochondrial fragmentation under hypoxia is controlled by down-regulation of PKA-dependent Drp1 phosphorylation [91]. Thus, fine-tuning of Drp1 activity by PKA is crucial for the adaptation of mitochondrial dynamics to the cellular metabolism in mammalian cells. However, it should be noted that additional protein kinases, phosphatases, sumo ligases, sumo proteases, and ubiquitin ligases contribute to the regulation of Drp1 activity [92,93], and other proteins, including mitofusins and Opa1, are subject to similarly complex post-translational modifications and transcriptional regulation. Thus, the coordinated action of multiple regulatory activities is required to shape the mitochondrial compartment.

6. Conclusions

Fusion and fission are antagonistic processes that predominate under different conditions to adapt mitochondrial morphology and dynamics to the bioenergetic requirements of the cell (Fig. 1). Fused mitochondria are preferred when optimal mitochondrial function is needed. Thus, fused mitochondrial networks are frequently found in respiratory active cells. Apparently, mixing of the matrix and the inner membrane allows the constituents of the respiratory machinery to cooperate most efficiently. Furthermore, fusion engages the entire mitochondrial compartment in respiration to maximize ATP synthesis. It is conceivable that the sudden need for metabolic energy is the reason for the formation of hyperfused mitochondrial networks that are formed upon exposure of cells to stress, and that fusion optimizes mitochondrial function during starvation. While fusion in stress-exposed or starving cells constitutes a short-term adaptation to changing environmental conditions, it also plays a beneficial role for maintenance of bioenergetic capacity in the long term. Upon aging, fusion allows complementation of gene products and thus compensates for the accumulation of mitochondrial mutations in heteroplasmic cells. Moreover, fused mitochondrial networks contribute to the dissipation of energy in large cells with a particularly high energy demand. In contrast, fragmented mitochondria are frequently found in resting cells and might represent a "default" morphological state when high respiratory activity is not required. The activity of the mitochondrial fission machinery contributes to maintenance of bioenergetic capacity as it allows the elimination of irreversibly damaged mitochondria by autophagy. The activity of the key proteins of mitochondrial dynamics is regulated at multiple levels, including transcription, post-translational modification, and direct response to the bioenergetic state of mitochondria.

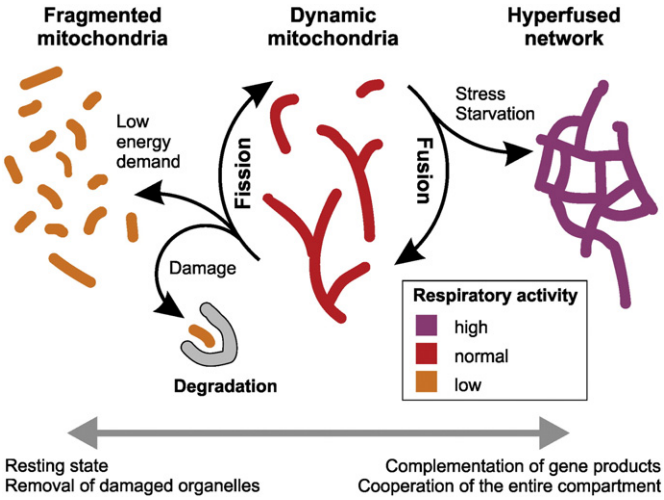

Fig. 1. Model of adaptation of mitochondrial morphology to respiratory activity. Fragmented mitochondria constitute the preferred morphological state when respiratory activity is low. Under respiratory conditions mitochondria undergo frequent cycles of fusion and fission to allow spreading of metabolites and macromolecules throughout the entire compartment. At the same time, mitochondrial fission is required for removal of damaged and inactive organelles by autophagy. When the bioenergetic state becomes critical, for example under nutrient deprivation or exposure to certain forms of stress, highly fused mitochondria are formed to optimize mitochondrial function. See text for details.

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