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Mitochondrial Division and Fusion in Metabolism

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Abstract

Mitochondria govern many metabolic processes. In addition, mitochondria sense the status of metabolism and change their functions to regulate energy production, cell death, and thermogenesis. Recent studies have revealed that mitochondrial structural remodeling through division and fusion is critical to the organelle's function. It has also become clear that abnormalities in mitochondrial division and fusion are linked to the pathophysiology of metabolic diseases such as diabetes and obesity. Here, we discuss the current understanding of the mechanisms of mitochondrial dynamics and their role in cellular and organismal metabolism.

Introduction

Popularly known as the "powerhouse of the cell", the mitochondrion is a double membrane-bound organelle and the source of cellular energy, ATP [1,2]. Cellular metabolism relies on mitochondria to provide energy from oxidative phosphorylation. Mitochondria are highly dynamic organelles that constantly fuse and divide to maintain normal cellular functions (Figure 1) [3-8]. When this delicate balance between division and fusion is lost, mitochondrial function, metabolism, and signaling are altered. A range of pathological conditions, including cancer, aging, neurodegeneration, and metabolic disorders have been associated with altering the balance between fusion and division [9-12]. Although many studies have sought to understand the dynamic nature of this process over the past several decades, the complete molecular mechanisms, physiological function, and connection to human diseases remain unclear.

Mitochondrial dynamics refer to the perpetual process of fusion, division, movement, and morphological changes which take place in response to the ever-changing physiological demands of cells [13,14]. There is dedicated protein machinery that controls the mitochondrial dynamics in the cell (Table 1) [6,15,16]. In this review, we focus on mitochondrial division and fusion. Division is crucial for maintaining the number of mitochondria in growing cells, regulating cell death pathways, and eliminating damaged

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mitochondria as part of quality control through mitophagy [7,17]. In contrast, fusion is important for mixing of mitochondrial contents and maintaining electrical conductivity throughout the mitochondria [17]. These two opposing forces ensure that at any given time, the cell has a healthy mitochondrial population. Defects in the core components of these systems, three dynamin-related GTPases, give rise to several disease conditions, including neonatal death with severe neural defects (defects in outer membrane protein Drp1, which mediates division), Charcot-Marie-Tooth neuropathy type 2A, a neurodegenerative disease of peripheral neurons, (defects in outer membrane protein Mfn2 which mediates fusion), and inherited forms of dominant optic atrophy (defects in inner membrane protein Opa1, which mediates fusion) [9,10,18].

It is well known that mitochondrial energy production controls cellular and organismal metabolism. Studies have shown that mitochondrial division and fusion regulate these metabolic processes, and changes in metabolism affect the dynamics of mitochondria. Therefore, the sensing and adjusting of metabolism by mitochondria create physiological circuits that consist of negative and positive feedback loops to establish robust metabolic responses. In this review, we discuss recent findings linking mitochondrial dynamics to metabolism.

Components of Mitochondrial Dynamics

Mitochondrial division

The dynamic nature of mitochondria was first observed during the early twentieth century [19,20]. Identification of the molecular components has been determined in approximately the last 15 years (Table 1) [6,15]. Model organisms have been instrumental in identifying the core components of mitochondrial division and fusion. Dnm1/Drp1 is the main component of mitochondrial division. It is a cytosolic dynamin-related GTPase, which moves to the mitochondrial outer membrane where it self assembles via GTP binding. Loss of Drp1 results in long interconnected mitochondrial networks. Mitochondrial receptors with transmembrane domains are involved in targeting Drp1 to the outer mitochondrial membrane. Yeast genetics was used to identify the central division component, Dnm1 [21,22], and its receptor Fis1 [23], and adaptors Mdv1 [24-26], and Caf4 [27]. Num1 and Mdm36 are unique, separate components with dual functions, connecting Dnm1 to the actin cortex and regulating both mitochondrial division and positioning within the cell [28-31]. Analyses of dynamin homologs in *Caenorhabditis elegans* and in mammalian cells have identified Drp1 (a homolog of Dnm1), and shown that Dnm1/Drp1 are evolutionarily conserved division factors [32,33]. A mammalian homolog of Fis1 has been identified [34]. However, Fis1 appears to recruit Drp1 in a subset of cell types, and/or under specific physiological conditions such as mitochondrial stress [35-37]. Steady state recruitment of Drp1 likely depends on other receptors such as Mff (mitochondrial fission factor) and Mid49/51 (MIEF1/2). Mff was discovered in siRNA screens, using cultured *Drosophila* DS2R+ cells [38,39], while Mid49/51 was found through analyses of mitochondrial proteomes [40,41]. The crystal structure and biochemical characteristics of Mid51 suggested that it binds to ADP and GDP [42,43]. Purified Mid51 stimulated the GTPase activity of Drp1 in the presence of ADP, suggesting that Mid51 sensed the metabolic status of cells and

regulated mitochondrial division [42,43]. Proteins that are involved in inner membrane fission are yet to be identified. However, it is likely that outer and inner membrane fissions are independent events which may be coordinated [18,32,44].

In addition to these mitochondrial components, the endoplasmic reticulum (ER) and actin cytoskeleton are also involved in mitochondrial division. ER tubules appear to encircle and constrict mitochondrial tubules prior to the recruitment of Drp1 to mitochondria [45]. At the inter-organelle interface, ER-associated formin, INF2, facilitates polymerization of actin to generate small patches of the actin cytoskeleton [46]. Other actin regulatory proteins such as cortactin, cofilin, and Arp2/3 complexes associate with mitochondria and regulate their division [47]. Myosin II is also assembled into filaments at the cytoskeleton and may form contractile networks to constrict mitochondrial tubules [48]. Interestingly, Drp1 receptors are located at the ER-mitochondria contact site, but in different manners. While a fraction of Mff is stably located at the organelle contact independently of Drp1, Mid proteins co-assemble with Drp1 [43,45]. Furthermore, Fis1 may be recruited to the contacts and form protein complexes with the ER proteins upon mitochondrial stress, possibly leading to mitophagy [36,37]. It would be important to understand how the actin cytoskeleton and Drp1 receptors interplay to coordinate Drp1 recruitment, assembly, and activation.

Mitochondrial fusion

Drosophila genetics discovered the first conserved fusion component, *fuzzy onions*, leading to subsequent identification of yeast (Fzo1) and mammalian homologs (Mfn1 and 2) (Table 1) [49-51]. *Drosophila fuzzy onions* is a developmentally regulated gene, and a homologous protein, Marf/Dmfn, was later found to be ubiquitously expressed [52]. Similar to Dnm1/Drp1, these proteins are dynamin-related GTPases. But unlike the division proteins, they have two transmembrane domains, which are embedded in the outer membrane and mediate fusion of the outer membrane. In addition to its role in membrane fusion, Mfn2 has also been shown to mediate membrane tethering of mitochondria with other organelles such as the ER [53] and melanosomes [54]. An inner membrane fusion component, Mgm1, was first identified in yeast, and later its mammalian homolog, Opa1, was characterized [55-59]. Mgm1 and Opa1 are also dynamin-related GTPases which are present in the inner membrane and the intermembrane space [60-64]. Interestingly, Mgm1/Opa1 has a role in the morphology of inner membrane cristae, which is important for the maintenance of the pro-apoptotic factor, cytochrome c, and the assembly of the electron transport chain complexes [65,66]. Studies of all these different organisms, along with the information from human diseases, have greatly helped elucidate the mechanism and function of the division and fusion machineries.

Metabolic control of mitochondrial dynamics

Mitochondria play a critical role in cellular bioenergetics by virtue of being the principal ATP generator in the cell. Cells sense changes in nutrient conditions and regulate mitochondrial ATP production to sustain normal physiology under stressful conditions such as starvation. Starvation induces autophagy, and mitochondria rapidly elongate in order to escape from being engulfed by autophagosomes, resulting in elimination by this quality control mechanism of the cell [67,68]. This elongation likely allows mitochondria to

maintain ATP production and is mediated by post-translational modifications of Drp1 through modulating its phosphorylation status [67,68]. When mitochondria become dysfunctional and are targeted for degradation by mitophagy, mitochondrial division generates small organelles to facilitate their movements and engulfment of mitochondria by autophagosomes [69-76].

In addition to Drp1, the function of Opa1 is regulated by the mitochondrial energetic status. In healthy cells, Opa1 produces two major forms (a membrane anchored form and a soluble form in the intermembrane space) by proteolytic cleavage of its transmembrane domain by the inner membrane located ATP-dependent proteases (m-AAA and i-AAA) [77,78]. However, when mitochondria decrease their function and membrane potential, Opa1 is excessively processed by a metalloproteinase (Oma1), releasing the majority of the protein from its transmembrane anchor, and becoming incompetent for fusion [79-82]. It is likely that combinations of increased division and decreased fusion may effectively produce small mitochondria, and separate them from the rest of the population. This proteolytic processing of Opa1 is further regulated by the level of oxidative phosphorylation. Oxidative phosphorylation stimulated Opa1-mediated inner membrane fusion [83]. Surprisingly, this oxidative phosphorylation stimulated fusion required the cleavage of Opa1 by Oma1 or Yme1L [83]. Uncleaved forms of Opa1 may undergo changes in the status of assembly or conformation upon proteolytic cleavage, which directly participate at a specific step in the pathway of mitochondrial fusion. Interestingly, when both proteases were lost in Oma1 or Yme1L knockout cells, Opa1 maintained the ability to fuse the inner membrane without proteolytic processing [84]. Therefore, its cleavage may not be an essential step, and may function in a specific type of fusion such as oxidative phosphorylation stimulated fusion. These new findings suggest elegant regulation of Opa1-mediated inner membrane fusion, which is a very active area of current research in the field of mitochondrial dynamics.

GTP is a major source for the energy that drives mitochondrial division and fusion, and Drp1, Mfn, and Opa1 are all dynamin-related GTPases. This suggests that the production of GTP is coupled to membrane remodeling. Nucleoside diphosphate kinases, which generate GTP from GDP and ATP, are important for dynamin-mediated membrane remodeling in endocytosis and mitochondrial fusion [85]. Two cytoplasmic nucleoside diphosphate kinases (NM23-H1/2) provide endocytic dynamin with GTP, while a mitochondrial counterpart (NM23-H4) supplies GTP for mitochondrial fusion. Because NM23-H4 interacts with Opa1, production of GTP may be spatially coupled with biding to Opa1 [86]. It is currently unknown whether NM23-H4 supplies GTP to other mitochondrial dynamin GTPases, Mfn1/2, and Drp1.

Diabetes and obesity

Diabetes mellitus is a chronic disease which affects ~400 million people worldwide. It is a disease where the body is either unable to produce enough insulin to deal with elevated blood glucose levels or is unable to respond to insulin which is produced and secreted by pancreatic β cells [5]. Pancreatic β cells normally control excess amounts of glucose by increasing their mass and producing and releasing increased insulin [5]. It has long been known that the most significant source of oxidative stress in a cell is mitochondria [87,88].

Recent studies have indicated abnormal mitochondrial dynamics in diabetic individuals along with increased reactive oxygen species (ROS) production [87,88]. Hyperglycemia induces excessive production of ROS, which strongly impacts mitochondrial morphology [88]. A study in diabetic mice showed increased mitochondrial fragmentation along with elevated Drp1 and decreased Opa1 levels [89]. This phenotype could be rescued with superoxide anion scavengers, indicating that ROS played important roles in failure of cellular bioenergetic control during hyperglycemia through regulation of mitochondrial division and fusion [89]. In diabetics, high glucose induced ROS generation can also cause endothelial dysfunction, where abnormal mitochondrial division is the cause [90]. Hyperglycemia also stimulated mitochondrial division in podocytes in the kidney by activating Drp1 under diabetic conditions [91]. The loss of mitochondrial fusion by Opa1 deficiency in pancreatic β cells also caused hyperglycemia, without inducing apoptosis or a loss of mtDNA in mice [92]. Therefore, mitochondrial dynamics might shift the balance to excess division under hyperglycemic conditions. Readjusting the balance of division and fusion might be beneficial, and inhibition of the division machinery partially ameliorated muscle insulin insensitivity and signaling in genetically obese mice [93]. These findings highlight the importance of mitochondrial division and fusion in glucose homeostasis, and the pathological consequences from imbalanced homeostasis caused by hyperglycemia.

Obesity has been linked to dysregulation of appetite which is controlled by leptin [94]. Leptin is secreted from adipocytes and signals neurons in the hypothalamus. Leptin resistance is a key component of obesity. In the hypothalamus, there are at least two types of neurons with opposite functions; orexigenic agouti-related protein (Agrp) neurons and anorexigenic pro-opiomelanocortin precursor (POMC) neurons. In orexigenic Agrp neurons of mice, mitochondria fragment upon starvation. In contrast, when mice are fed with high fat diets, mitochondria elongate in a manner dependent on Mfns [95]. When Mfns were deleted, Agrp neurons decreased their firing frequency in response to high fat diets, perhaps due to decreased intracellular ATP levels, as the addition of exogenous ATP restored the defects in mitofusin-depleted Agrp neurons [95]. These changes in mitochondrial dynamics are important for the physiological control of metabolism and body weight. Although the mechanisms remain unclear, the mitochondrial fusion and division machinery may function to control appetite in leptin-mediated and diet-regulated signaling pathways in neurons. It is also possible that changes in mitochondrial dynamics affect respiratory functions and modulate intracellular ATP levels which, in turn, affect neuronal activities. In POMC neurons, abundance of Mfn2 decreased in diet-induced obese mice, leading to fragmentation of mitochondria, decreases in ER-mitochondria contacts, and ER stress [96]. These mice became resistant to leptin and increased their body weight. Interestingly, modest overexpression of Mfn2 decreased food intake and body weight in mice fed with high fat diets. Knockout of Mfn2 in POMC neurons led to phenotypes similar to those found in diet-induced obese mice, suggesting the pathological mechanisms underlying diet induced obesity involved changes in Mfn2, mitochondrial fusion, and mitochondria-ER interactions [96].

In addition to these neurons, mitochondria in adipocytes also changed their dynamics, and therefore their functions in thermogenesis. In brown adipocytes which control body temperature, the sympathetic neurotransmitter norepinephrine induced fragmentation of

mitochondria by activating Drp1 and inactivating Opa1 [97]. This fragmentation promoted energy expenditure by inhibiting oxidative phosphorylation and enhancing heat production. It is possible that mitochondrial division and fusion in different parts of the body sense nutrient availability and respond to hormones to physiologically regulate metabolism.

Conclusions and Future Directions

Mitochondrial dynamics play an integral role in cellular and physiological remodeling of mitochondrial structure and function in response to metabolic changes. Dysregulation of these membrane remodeling processes can result in pathological conditions, including metabolic disorders. We anticipate that the list of diseases related to metabolic alterations controlled by mitochondrial division and fusion will expand as increased knowledge of the mechanistic links of these processes to diseases becomes available. For example, changes in mitochondrial morphology and respiration are associated with different types of cancers. However, it is unclear how mitochondrial division and fusion are involved in tumorigenesis. Mitochondria also remodel their structural organization and functional capacity during development of the cardiac, immune, and nervous systems, suggesting that abnormalities in mitochondrial division and fusion can contribute to developmental disorders in multiple tissues. Finally, understanding the mechanisms underlying age-related declines in mitochondrial function and disorganization in their structures will be an exciting topic for future studies.

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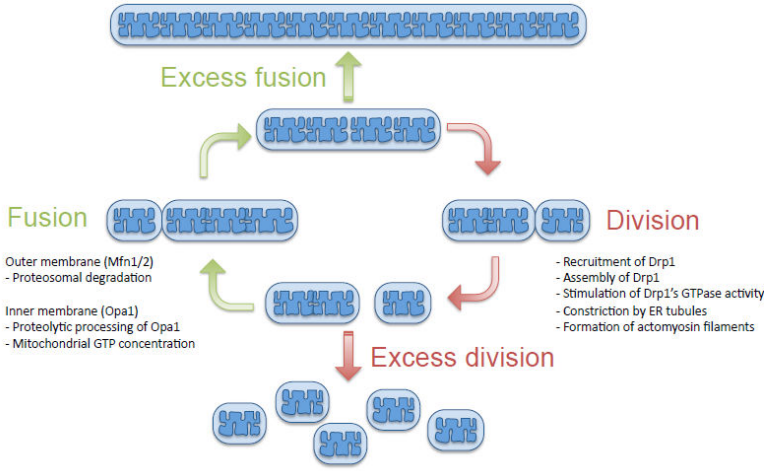

Figure 1. Mitochondrial morphology is regulated by division and fusion

Mitochondria continuously divide and fuse and control their morphology. Mitochondrial division is initiated by recruitment of cytosolic Drp1 to the mitochondrial outer membrane by Drp1 receptors. On mitochondria, Drp1 assembles into helical filaments, wrapping around mitochondrial tubules. Drp1 filaments constrict and divide mitochondria, working together with ER tubules and actomyosin filaments. Mitochondrial fusion consists of outer membrane fusion and inner membrane fusion. Outer membrane fusion is mediated by mitofusin while inner membrane fusion is mediated by Opa1. Mitochondrial fusion is regulated by proteosomal degradation of mitofusins, proteolytic processing of Opa1 and production of GTP.

Table 1

Key proteins involved in mitochondrial dynamics and associated disease. Main components of the mitochondrial fusion and fission machineries are indicated in model organisms from algae to mammals. Their location, functions and related diseases are shown.

Key Mitochondrial dynamics proteins	Algae	Yeast	Worms	Fly	Mammals	Function	Disease
Dynamin related protein1 (Drp1)	Dnm1	Dnm1	DRP-1	Drp1	Drp1	OM Fission	Post neonatal death with neurodevelopmental defects
Mitochondrial fission factor (Mff)	Unknown	Unknown	Mff-1	Mff-1	Mff	Drp1 receptor	Unknown
MiD49/MiD51	Unknown	Unknown	Unknown	Unknown	Mid49/Mid51	Drp1 receptor	Unknown
Fission Protein 1 (Fis1)	Fis1	Fis1	Fis-1	Fis1	Fis1	Drp1 receptor	Unknown
Mdv1/Caf4/Num1/ Mdm36	Mda1/-/-/-	Mdv1/Caf4/Num1/Mdm36	Unknown	Unknown	Unknown	Dnm1 adaptor protein	Unknown
Ganglioside induced differentiation protein (GDAP1)	Unknown	Unknown	Unknown	CG4623?	GDAP1	Unknown	Charcot-Marie-Tooth type 4A
Optic atrophy 1 (Opa1)	Mgm1	Mgm1	EAT-3	Opa1	Opa1	IM Fusion	Autosomal dominant Optic atrophy type 1
Mitofusin1/2 (Mfn1/2)	Fzo1	Fzo1	Fzo-1	Fzo1, Marf, dMfn	Mfn1/Mfn2	OM fusion	Charcot-Marie-Tooth type 2A
Ugo1	Ugo1	Ugo1	Unknown	Unknown	Unknown	OM fusion Links Fzo1 and Mgm1	Unknown