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Review

Interfaces between mitochondrial dynamics and disease

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ABSTRACT

In the cellular context, mitochondria display a number of dynamic behaviors including fusion, division (or fission), directed transport, and targeted destruction (mitophagy). The relevance of these processes to human diseases has been intensively studied over the last several years, and emphasize the importance of mitochondrial dynamics to the central nervous system. Intriguingly, a common theme is that these behaviors do not function in isolation, but influence one another either directly or indirectly. Here, we review the dynamic properties of mitochondria and summarize their relationships to human diseases.

Contents

1. Introduction

While the bioenergetic functions of the mitochondrion have been investigated for many years, an appreciation of their dynamic behavior has only recently arisen. Initial static observations indicated that mitochondria adopt a variety of shapes and localization within a cell, and also interact with each other and other organelles, such as lipid droplets and the endoplasmic reticulum (ER). Live cell imaging has solidified the dynamic nature of the organelle in various cell types and, with the identification of the key effector proteins, genetic studies have highlighted the relevance of mitochondrial dynamics to human disease. In particular, alterations in mitochondrial dynamics have been reported in numerous ailments ranging from cancer to neurodegeneration, and genetic defects in mitochondrial dynamics are also directly responsible for a subset of neurodegenerative diseases.

How disturbances in mitochondrial dynamics impact the disease state is still under intense scrutiny, and multiple hypotheses have been proposed. Since the organelle has many biochemical functions, each of which is potentially impinged upon by alterations in dynamics, it has been difficult to succinctly describe how a defect in behavior might lead to disease. It appears that the situation may be considerably complex, depending on the cell type and disease context, and even the precise mutation within the gene. Some examples of processes that may be altered include ROS production, Ca^{2+} handling and ER stress, ATP production, mislocalization of the organelle, apoptosis, innate immunity, and altered mitophagic fluxes. Intriguingly, mutations in mitochondrial dynamics genes (Table 1) particularly affect the nervous system, often causing progressive neuronal degeneration in various types of neurons. In this review, we will describe the dynamic processes that the mitochon-

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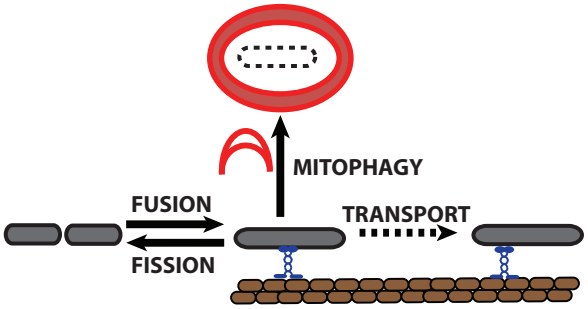

Fig. 1. Schematic overview of mitochondrial dynamics.
The mitochondrial network is known to display several dynamic behaviors including shape changes due to fusion and fission, as well as directed transport (mediated by motor proteins), and mitophagy, targeted destruction via autophagosomal membranes (shown in red).

drion undergoes, and emphasize the current relationships between these behaviors and disease.

2. Overview of mitochondrial dynamics

It is readily apparent from time-lapsed imaging that mitochondria are motile and dynamic, undergoing multiple complex behaviors including movement and shape changes. Methods to deconvolute individual behaviors have been developed; in particular, the use of photo-activatable and photo-convertible fluorescent proteins allows tracking of individual organelles within the entire mitochondrial population [47,64,81]. To this end, it has been useful to classify their behaviors into distinct processes that can be studied individually (Fig. 1). We can divide mitochondrial dynamics as follows: (1) fusion (the joining of two organelles into one); (2) fission (the dividing of a single organelle into two); (3) transport (directed movement of an organelle along a cytoskeletal element); and (4) mitophagy (targeted destruction of an organelle via the autophagic machinery).

3. Mitochondrial fusion

Although mitochondrial fusion can be simply defined as the joining of two organelles into one, it requires the coordination of two distinct steps: fusion of the outer membrane followed by fusion of the inner membrane (Fig. 2A). Fusion of the outer membranes is mediated by the mitofusin proteins (Mfn1 and Mfn2), localized to the mitochondrial outer membrane. These proteins are members of the dynamin superfamily of large GTPases, and were first identified in *Drosophila melanogaster* as important for spermatogenesis [32]. Genetic studies have now implicated mitofusin 2 as the gene mutated in Charcot-Marie Tooth (CMT) Syndrome type 2A, characterized by neuronal degeneration of long sensory and motor neurons [39,93], as well as hereditary motor and sensory neuropathy (HMSN) type VIA [92]. Mutations in mitofusin 1 have not yet been implicated in human disease.

Genetic deletion of the mitofusin proteins results in the complete absence of fusion and causes clear defects in the organelle population in both culture and tissues [10,11,14,15,70]. The defects are characterized by a loss of cristae ultrastructure and mitochondrial membrane potential, depletion of mitochondrial DNA (mtDNA), as well as an increased mutational load in the mitochondrial genome (in tissues). The data strongly implicates the fusion process as critical for the health of the organelle population and fidelity of the mitochondrial genome, and complete loss of fusion is embryonic lethal in mice.

The direct relevance of mitochondrial fusion to CMT and human diseases is more complicated, as mitofusin 2 has also been implicated in other physiologic processes including transport, as well as ER tethering and calcium handling [19,24,55]. Indeed, several neuronal models of mitofusin 2 deficiency (in Purkinje cells, DRGs, and dopaminergic neurons) present with distal axonal degeneration associated with decreased anterograde transport of mitochondria, lower axonal and synaptic densities of mitochondria, and accumulation of organelles within the cell soma (Fig. 2B) [5,12,65]. The degeneration is predominantly axonal in nature, and consistent with a decreased number of mitochondria in axonal synapses. Tracking studies implicate deficiencies in transport, as opposed to fusion, consistent with the idea that the mitofusins interacts with the transport machinery [55]. In contrast, mitofusin 1 knockout studies show no particular neuronal phenotypes, though this may be due to a lack of expression in these cell types [12]. In other neurons, Mfn2 depletion results in ER-stress associated with decreased neuropeptide production [71]. Thus, we would conclude that much of the disease pathology in CMT 2A patients is attributable to organellar effects separate from fusion. Indeed, several mitofusin 2 mutations found in patients show no apparent fusion defect *in vitro* [21].

Fusion of the mitochondrial inner membrane is mediated by the intermembrane space protein Opa1, another member of the dynamin superfamily that is localized to the mitochondrial inner membrane. In humans, mutations in Opa1 cause autosomal dominant optic atrophy (ADOA), characterized by progressive blindness and the degeneration of retinal ganglion cells and the optic nerve [1,20]. Similar to many mitochondrial inner membrane proteins, Opa1 has an interesting primary structure consisting of an N-terminal mitochondrial targeting sequence (MTS) and transmembrane domain. While the MTS is constitutively cleaved upon import into the organelle, an N-terminal transmembrane domain remains and anchors this form to the membrane, referred to as the long-form. However, two proteases (Oma1 and Yme1L) have the capacity to cleave Opa1 from its N-terminal transmembrane domain, producing a short, soluble form that has a more characteristic topology to other dynamin family members (Fig. 2A,C). These proteases appear to be highly regulated, responding to various aspects of mitochondrial biology. Oma1 is strongly activated by depolarization of the inner membrane, as well as apoptotic stimuli; while Yme1L activity can be controlled by ATP levels, mitochondrial oxidative phosphorylation (OXPHOS) and translational stress [23,36,54,68]. These mechanisms allow tuning of mitochondrial fusion rates to the organellar and cellular bioenergetics. In particular, it appears that a balance of long and short forms of Opa1, as well as proteolysis itself is required for fusion activity [52,54,76], although recent studies have challenged this viewpoint and implicated long Opa1 as the primary fusion mediator [4].

Besides its role in fusion, Opa1 has also been implicated in several other mitochondrial properties including apoptosis, cristae ultrastructure, and stability of respiratory supercomplexes [18,27,61]. Opa1-null cells exhibit severe defects in all of these characteristics, as well as inner membrane fusion [77]. Thus, similar to mitofusin-2 associated diseases, it is not clear whether ADOA can be primarily attributed to a defect in mitochondrial fusion, as opposed to one or a combination of these other processes. The selectivity of the disease for the optic nerve resembles that of certain mtDNA diseases (Leber's Hereditary Optic Neuropathy (LHON) [8]), suggesting that abnormalities in mitochondrial OXPHOS may underlie the pathology in ADOA. Indeed, both diseases (LHON and ADOA) are characterized by an apoptotic death of retinal ganglion cells, though the timing of the disease is quite dissimilar. In addition, some mutations in Opa1, particularly those localized the G domain, result in a more systemic disease (DOA-plus), and DOA-plus tissues have a prevalence of deletions in mtDNA [3,35,90], a phenotype reminiscent of fusion deficiency [14]. Further work using animal models