CellPress

Review

Mitochondrial Dynamics and Metabolic Regulation

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Mitochondrial morphology varies tremendously across cell types and tissues, changing rapidly in response to external insults and metabolic cues, such as nutrient status. The many functions of mitochondria have been intimately linked to their morphology, which is shaped by ongoing events of fusion and fission of outer and inner membranes (OM and IM). Unopposed fission causes mitochondrial fragmentation, which is generally associated with metabolic dysfunction and disease. Unopposed fusion results in a hyperfused network and serves to counteract metabolic insults, preserve cellular integrity, and protect against autophagy. Here, we review the ways in which metabolic alterations convey changes in mitochondrial morphology and how disruption of mitochondrial morphology impacts cellular and organismal metabolism.

Trends

Mitochondrial morphology varies widely across different cell types and tissues and results from the opposing and coordinated forces of mitochondrial fission and fusion of OMs and IMs.

The regulation of fusion and fission is manifold and responds rapidly to metabolic cues.

The fusion and fission machinery is essential for life, and genetic ablation of individual components in adult tissues impairs organ function and whole-body metabolism.

Interpreting the relevance of mitochondrial morphology is complicated by the functional redundancy and additional roles that these components have within as well as outside mitochondria.

Mitochondria Forms and Functions

The need for mitochondria in healthy tissues is ubiquitous, yet the emphasis placed on the various metabolic functions they perform varies across tissues. The morphology of mitochondria is inextricably linked to its functions, which include the production of ATP by **oxidative phosphorylation** (OXPHOS; see Glossary), regulation of programmed cell death, calcium homeostasis, and the generation and control of reactive oxygen species (ROS) [1]. Balanced fusion and fission events shape mitochondria to meet metabolic demands and to ensure removal of damaged organelles. The dynamism of mitochondria is highlighted by the dramatic changes in morphology that they undergo in response to metabolic inputs (Figure 1) [2]. Mitochondrial fragmentation occurs in response to nutrient excess and cellular dysfunction, and has been observed in cardiovascular and neuromuscular disorders, cancer, and obesity. It facilitates the autophagic clearance of mitochondria (**mitophagy**; reviewed elsewhere [3]) and allows the adaption of mitochondrial activities to physiological demands. While ultrastructural changes have long been observed in response to alterations in oxidative metabolism [4], it has become increasingly clear that mitochondrial shape changes can also have dramatic effects on the cellular metabolism. In this review, we summarize recent evidence that highlights the functional interrelation of mitochondrial dynamics and metabolism.

The Molecular Machinery of Mitochondrial Dynamics

With pioneering studies in yeast leading the way, the past 15 years of research have identified the machinery of mitochondrial fusion and fission (Figure 2). Mechanistic insight into the physiological relevance of mitochondrial dynamics has come from the study of patients harboring genetic lesions in components of either fusion (*MFN2* and *OPA1*) or fission (Dynamin-related protein 1; *DRP1*) [5], which cause mitochondrial fragmentation and hypertubulation, respectively. We first introduce critical mammalian components of fusion and fission machineries and their regulation at various layers (transcription, post-translational modifications, and proteolysis), before discussing how their function is intertwined with metabolism.

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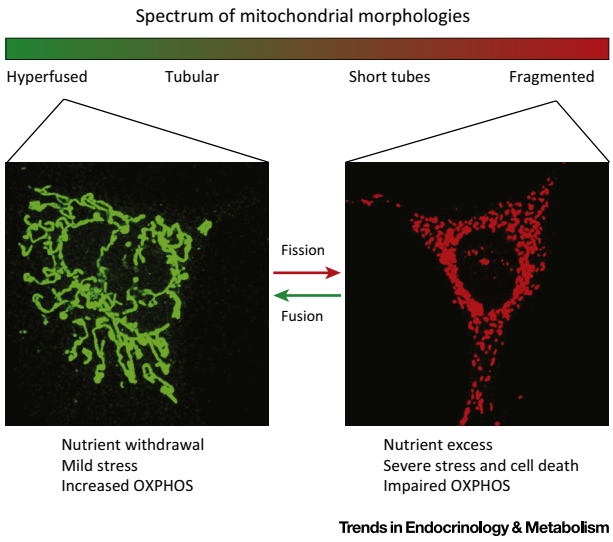

Figure 1. Metabolic Inputs Modulate Mitochondrial Morphology. The morphology of mitochondria can vary significantly over a wide range and is influenced by metabolic stimuli in cultured cells (mouse embryonic fibroblasts) to adopt a hyperfused (green) or fragmented (red) morphology. Abbreviation: OXPHOS, oxidative phosphorylation.

Fusion Machinery of the Outer Membrane

Mitofusins

Dynamin-like GTPases mediate the fusion of both mitochondrial OMs and IMs. The mammalian orthologs mitofusin 1 and mitofusin 2 (*Mfn1* and *Mfn2*) orchestrate OM fusion and are required for the maintenance of a reticular mitochondrial network in cells [6]. Both proteins contain conserved catalytic GTP-binding domains at the N termini and are anchored to the OM by C-terminal transmembrane domains (Figure 2). Mitofusins mediate OM fusion by homo- and heterotypic interactions that depend on GTP hydrolysis. Mitofusin synthesis is regulated by transcriptional and post-transcriptional mechanisms, while proteasome-mediated degradation is regulated by **ubiquitylation** and phosphorylation (Box 1). Deletion of either *Mfn1* or *Mfn2* or abrogation of GTPase activity prevents mitochondrial fusion, causing the network of cultured cells to fragment in the face of unopposed mitochondrial fission [6]. *In vivo*, deletion of either mitofusin causes embryonic lethality in mice [7], but both proteins appear to be functionally redundant in some adult tissues. In humans, pathogenic mutations in *MFN2* (but not *MFN1*) cause **Charcot-Marie-Tooth type 2A** (CMT2A) disease, which is a peripheral neuropathy characterized by axonal degeneration and distal muscular atrophy [5]. CMT2A shows various modes of transmission, although a gain-of-function mechanism has been proposed to explain autosomal dominant inheritance of *MFN2* GTPase mutations [8]. Transgenic mice engineered to express one such mutation (T105M) specifically in motor neurons elicited neuromuscular defects similar to those observed in patients with CMT2A [9]. Tissue-specific deletion of mitofusins in the central nervous system, heart, muscle, or liver compromise metabolic and organ function, highlighting their importance at both the cellular and organismal level [10,11].

mitoPLD

The importance of modulating mitochondrial phospholipids during the process of membrane fusion was highlighted by the discovery of mitoPLD, a member of the phospholipase D family [12]. MitoPLD (encoded by *Pld6*) is bound to the OM through a C-terminal transmembrane anchor with an N-terminal catalytic domain facing the cytosol. MitoPLD is capable of converting **cardiolipin** (CL) to **phosphatidic acid** (PA), and this catalytic activity is required for mitochondrial fusion. Intriguingly, PA recruits the PA phosphatase Lipin 1b to the mitochondrial surface, where it converts PA to diacylglycerol (DAG), which blunts the profusion effects of PA [13]. Ablation of mitoPLD causes mitochondrial fragmentation *in vitro* and impinges upon germline development and fertility in mice and flies [13,14]. Recently, a novel phospholipase PA-PLA1

Glossary

Agouti-related peptide (AgRP): a peptide produced by specific hypothalamic neurons; AgRP increases appetite and promotes feeding behavior while reducing energy expenditure.
Autosomal dominant optic atrophy (ADOA): inherited bilateral degeneration of the optic nerve caused by mutations in Opa1 and the most common autosomally inherited optic atrophy.
Cardiolipin (CL): a nonbilayer-forming phospholipid unique to mitochondria that is required for the optimal function of multiple enzymes at the IM and for fusion at the OM.
Charcot-Marie-Tooth type 2A (CMT2A): a hereditary motor and sensory neuropathy belonging to the most common class of inherited neurological disorders. Type 2A is caused by mutations in Mfn2.
Mitochondrial unfolded protein response (UPR-mt): a stress program characterized by the transactivation of mitochondrial chaperone and protease genes.
Mitophagy: autophagic removal of defective or dysfunctional mitochondria. Several pathways exist, with the most notable being the PINK-PARKIN pathway. Dissipation of the mitochondrial membrane potential causes PINK1 to translocate to the OM, where it is recognized by the E3 ubiquitin ligase PARKIN, which helps target the marked organelle for lysosomal degradation.
Oxidative phosphorylation (OXPHOS): electron transfer along the respiratory chain complexes (I–IV) in the IM generating a proton gradient that is harnessed by ATP synthase (complex V) to produce ATP from ADP and inorganic phosphate.
Parkinson's disease (PD): neuromuscular disorder characterized by dopamine deficiency and basal ganglia degeneration. Mutations in *PARK2* (which encodes PARKIN) and *PINK1* cause early-onset PD.
Peroxisomes: single membrane-bound organelles responsible for fatty acid oxidation, ether phospholipid biosynthesis, and ROS metabolism.
Phosphatidic acid (PA): a nonbilayer forming cardiolipin precursor that also serves as a signaling molecule.
Pro-opiomelanocortin (POMC): a precursor neuropeptide that is