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The complex interplay between mitochondrial dynamics and cardiac metabolism

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Abstract

Mitochondria are highly dynamic organelles, capable of undergoing constant fission and fusion events, forming networks. These dynamic events allow the transmission of chemical and physical messengers and the exchange of metabolites within the cell. In this article we review the signaling mechanisms controlling mitochondrial fission and fusion, and its relationship with cell bioenergetics, especially in the heart. Furthermore we also discuss how defects in mitochondrial dynamics might be involved in the pathogenesis of metabolic cardiac diseases.

Keywords

Heart; Metabolism; Mitochondria; Mitochondrial dynamics; Fusion; Fission

Mitochondrial dynamics

During the last 5 decades the concept of mitochondria as static organelles has changed to appreciate their highly dynamic nature, including their ability to modify their morphology, subcellular distribution and activity by fusion and fission events (Osteryoung and Nunnari 2003; Chen and Chan 2004; Berman et al. 2008). Through these processes the mitochondria may adopt different morphologies in response to internal and external signals. For example, in interphase HeLa cell mitochondria form long tubular structures. These structures, in turn, fragment during early mitotic phase to facilitate segregation of mitochondria in daughter cells (Taguchi et al. 2007). In apoptotic cell death, fragmentation of the mitochondrial network can be a requisite step for the release of cytochrome c (Youle and Karbowski 2005); and the elongation of mitochondrial tubules has been observed during differentiation of embryonic stem cells into cardiomyocytes, possibly in response to an increase in energy demand from nascent sarcomeres (Chung et al. 2007).

Mitochondrial fission and fusion molecular core machinery

In mammalian cells, the main regulators of mitochondrial fusion are the dynamin-related GTPases mitofusin (MFN) and optic atrophy protein 1 (OPA1) (Meeusen et al. 2006; Song et al. 2009). Mammalian cells express two isoforms of MFN (MFN1 and MFN2), both localized in the outer mitochondrial membrane (OMM) with the N-terminal (GTPase domain) and C-terminal (coiled-coil region) domains protruding into the cytosol. MFN1 and MFN2 interact with their homologous proteins in adjacent mitochondria to coordinate OMM fusion (Legros et al. 2002; Rojo et al. 2002; Chen et al. 2003). OPA1, localized in the inner mitochondrial membrane (IMM), is required to tether and fuse the IMM and also participates in cristae remodeling, an important determinant of mitochondrial metabolism (Olichon et al. 2002; Frezza et al. 2006; Meeusen et al. 2006).

The mitochondrial fission 1 protein (FIS1) and Dynamin-related protein 1 (DRP1) are involved in mitochondrial fission. While FIS1 is a single-pass transmembrane protein anchored to the OMM by its C-terminal region, DRP1 is located in the cytosol and recruited to mitochondria during fission. In yeast, DRP1 recruitment depends on its binding to FIS1 (Tieu et al. 2002; Griffin et al. 2005). Although a direct *in vivo* interaction between DRP1 and FIS1 has not been demonstrated in mammalian cells, both proteins are required for mammalian mitochondrial fission (Yoon et al. 2003; Chen and Chan 2005).

Metabolism and mitochondrial dynamics

Several reports have demonstrated a direct correlation between the extent of mitochondrial fusion and the capacity for oxidative phosphorylation (OXPHOS) (Pich et al. 2005; Zanna et

al. 2008). Improved physical continuity of a fused mitochondrial network may facilitate propagation of the mitochondrial membrane potential (ΔΨt) and diffusion of metabolites. Evidence of such a relationship between mitochondrial morphology and function derives from studies showing that inhibition of fusion results in reduced oxygen consumption and a loss of ΔΨt (Chen et al. 2003; Chen and Chan 2005). There is a close relationship between cell metabolic status and mitochondrial morphology. Silencing of *MFN2* substantially impairs pyruvate, glucose, and fatty acid oxidation (Pich et al. 2005); consistent with this, there is a marked reduction in MFN2 levels in skeletal muscle from both obese humans and animal models of obesity. Conversely, *MFN2* over-expression evokes increases in respiratory complex activity, glycolysis and mitochondrial biogenesis (Bach et al. 2005; Pich et al. 2005; Soriano et al. 2006). Interestingly, *MFN2* expression is up-regulated in conditions of high energy demand (i.e. exercise or cold exposure) or in response to pro-apoptotic stimuli which elicit a rapid stress-induced mitochondrial hyperfusion coupled with a transient increase in mitochondrial ATP production (Tondera et al. 2009). Similar to changes in MFN2 levels, decreased OPA1 levels lead to mitochondrial fragmentation, decreased oxygen consumption, and ΔΨt dissipation. Dysregulation of OPA1 has been also implicated in the pathogenesis of neurodegenerative diseases and heart failure (Bossy-Wetzel et al. 2003; Chen et al. 2009).

Mitochondrial fission also plays a key role in cell metabolism. In this way, hyperglycemia induces fission of the mitochondrial network; and the inhibition of this process by a dominant negative form of DRP1 markedly impairs mitochondrial ability to increase respiratory rate under these conditions (Yu et al. 2006). Taken together, these results reinforce the concept that mitochondrial plasticity is critical for cell metabolic adaptation, particularly in those tissues with high energy demand and oxidative capacity (Soubannier and McBride 2009).

At the molecular level, the GTP requirement of the effector proteins OPA1, MFN1, MFN2 and DRP1 may provide a direct link between the cell's bioenergetic state and mitochondrial morphology, as most GTPase activities depend indirectly on the overall ATP content.

Regulatory control of mitochondrial dynamics can be exerted through a series of post-translational modifications described for DRP1, OPA1 and MFN2 (Ishihara et al. 2003; Braschi et al. 2009; Figueroa-Romero et al. 2009). In addition, regulation of OPA1 function involves proteolytic processing into short and long isoforms (Griparic et al. 2007; Song et al. 2007); both cleavage products are needed to preserve mitochondrial fusion under normal conditions (Soubannier and McBride 2009). Loss of ΔΨt can promote further OPA1 cleavage and proteolysis causing suppression of OPA1 function (Griparic et al. 2007; Song et al. 2007). This reduces the propensity of the mitochondria to fuse leading to isolation of the depolarized mitochondrion and its damaged contents from the network (Legros et al. 2002) (Fig. 1).

Cardiac metabolism, mitochondrial morphology and diseases

Under normal conditions, 70% of the ATP production in adult cardiomyocytes derives from fatty acid β-oxidation (van der Vusse et al. 2000). This process is closely regulated by carnitine palmitoyltransferase I (CPT1), the enzyme which facilitates acyl-CoA import across the outer mitochondrial membrane (Marin-Garcia 2003; Saks et al. 2006). Mitochondrial pyruvate dehydrogenase (PDH) is a key regulatory point in glycolysis and its activity increases in response to increased ATP demand via a variety of mechanisms, including an elevation in mitochondrial calcium levels, increasing the contribution of glycolysis to cardiomyocyte metabolism (Sharma et al. 2005). Likewise, an increase in mitochondrial calcium content can increase the activity of several dehydrogenases in the

tricarboxylic acid cycle (TCA). Mitochondrial calcium levels are in turn dependent on the character of the cytoplasmic calcium transients evoked by cardiomyocyte contraction (Hansford 1987). This allows an appropriate coupling between contractile function and energy supply (Denton and McCormack 1990; Liu and O'Rourke 2009). Tissues with high energy requirements (e.g. heart and skeletal muscle) have a predominantly fused mitochondrial morphology with tightly packed cristae, while low energy demanding tissues (e.g. liver) tend to manifest a fissioned state and tend toward less dense packing of cristae (Duchen 2004; Kodde et al. 2007).

As above, a continuous balance between mitochondrial fission and fusion is critical for maintaining proper mitochondrial function. However, in cardiac myocytes, this important issue has only recently begun to be addressed, possibly due to the general perception that the highly structured organization of adult ventricular cardiomyocytes prevents mitochondrial dynamics from playing a relevant role (Hom and Sheu 2009). Interestingly, cardiac tissue contains higher levels of many of the proteins involved in mitochondrial dynamics than other tissues (Imoto et al. 1998; Bach et al. 2003; Stojanovski et al. 2004; Parra et al. 2008; Iglewski et al. 2010). Further, both hyper- and hypo-fusion of cardiac mitochondria have been observed in association with pathological conditions. Notably, more than 40 years ago, Sun et al. showed that hypoxia results in the formation of giant mitochondria in perfused hearts (Sun et al. 1969). More recently, Shen et al. have shown that MFN2 is a determinant of oxidative stress-dependent cardiomyocyte apoptosis (Shen et al. 2007). Similarly, Reicherts et al. reported the participation of OPA1 in the degradation of dysfunctional mitochondria in myopathic hearts (Duvezin-Caubet et al. 2006). An even more interesting relationship is found in the diabetic heart. Recent in vitro data suggest that hyperglycemia induces mitochondrial fragmentation, resulting in cell death (Yu et al. 2006). Makino et al. demonstrated that coronary endothelial cells from murine diabetic hearts displayed mitochondrial fragmentation associated with reduced levels of OPA1 and increased levels of DRP1 (Makino et al. 2010). These data suggest a role for mitochondrial fusion and fission in the pathogenesis of diabetic cardiomyopathy; however, a full understanding of the contribution of mitochondrial dynamics to cardiac function is lacking.

Perspectives

During the last decade the complex processes of mitochondrial dynamics have been the object of intense scientific inquiry. Great strides have been made in our understanding of the intricate molecular mechanisms that control mitochondrial fusion and fission. A fundamental connection between remodeling of mitochondrial architecture and changes in metabolism is well established, and the importance of this relationship for growth and survival demonstrated in many different tissue types is clear. In the heart, these aspects are just beginning to be studied, but it is already apparent that the mitochondrial network is not static in adult cardiac myocytes as previously assumed. Future studies aimed to fully elucidate the relationship between mitochondrial morphology, metabolism, and cardiac function will provide new insights for the prevention and treatment of cardiovascular disease.

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Abbreviations

MFN	Mitofusin
OPA1	optic atrophy 1 protein
OMM	outer mitochondrial membrane
IMM	inner mitochondrial membrane
Fis1	mitochondrial fission 1 protein
Drp1	dynamin related protein 1
$\Delta\Psi_m$	mitochondrial membrane potential
OXPHOS	oxidative phosphorylation
CPT1	carnitine palmitoyl transferase 1
PDH	pyruvate dehydrogenase
TCA	tricarboxylic acid cycle

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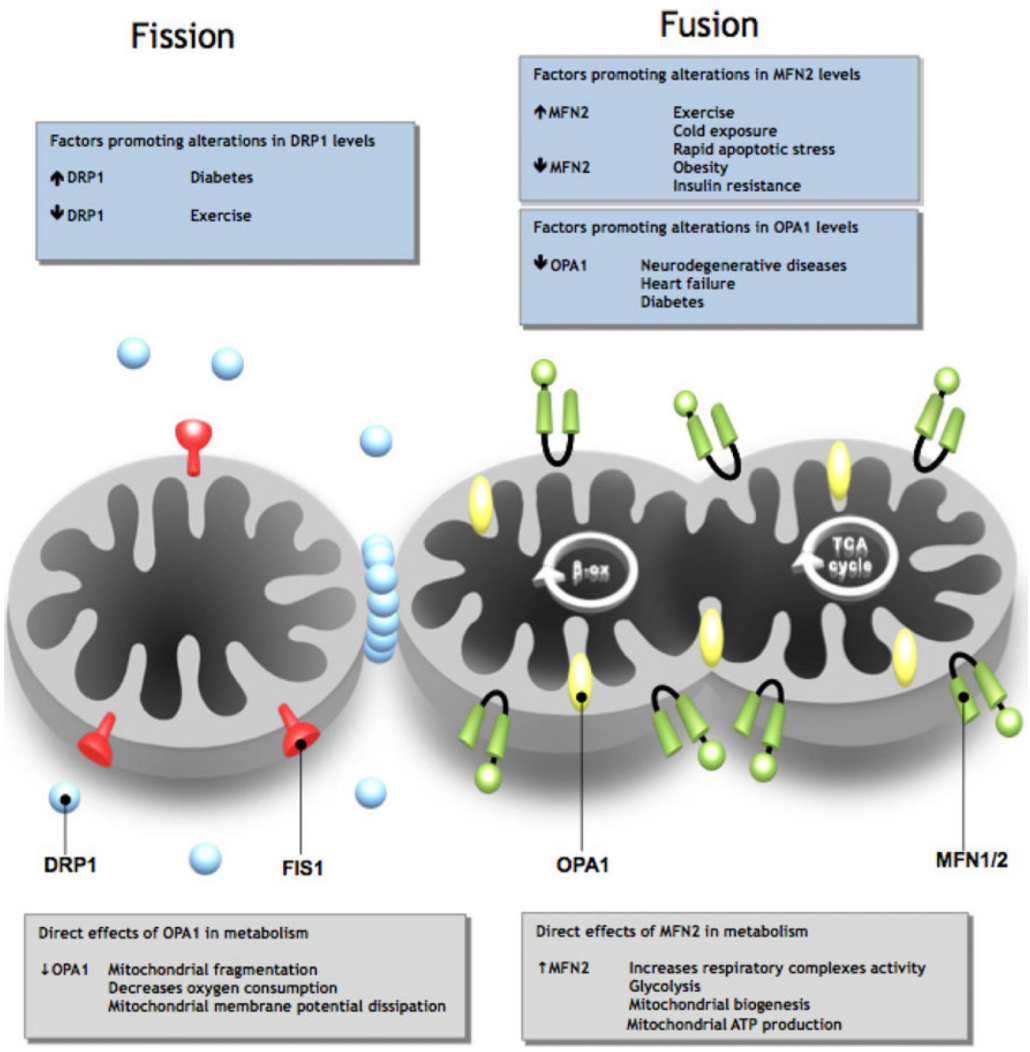

Fig. 1.

Potential roles of mitochondrial dynamics in cardiac metabolism. Factors regulating mitochondrial fission and fusion are depicted at the left and right side of the figure, respectively. . DRP1: Dynamin-related protein 1. FIS1: Fission protein 1. OPA 1: Optic atrophy protein 1. MFN1/2 : Mitofusin 1/2. TCA cycle: Tricarboxylic acid cycle. B-ox: Fatty acid beta oxidation.