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Mitochondrial fusion and fission proteins as novel therapeutic targets for treating cardiovascular disease

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ABSTRACT

The past decade has witnessed a number of exciting developments in the field of mitochondrial dynamics – a phenomenon in which changes in mitochondrial shape and movement impact on cellular physiology and pathology. By undergoing fusion and fission, mitochondria are able to change their morphology between elongated interconnected networks and discrete fragmented structures, respectively. The cardiac mitochondria, in particular, have garnered much interest due to their unique spatial arrangement in the adult cardiomyocyte, and the multiple roles they play in cell death and survival. In this article, we review the role of the mitochondrial fusion and fission proteins as novel therapeutic targets for treating cardiovascular disease.

1. Introduction

In the heart, the mitochondria occupy nearly one third the volume of a cardiomyocyte – they sustain the energy required for normal cardiac contractile function by producing up to 30 kg of adenosine triphosphate (ATP) per day. However, the role of cardiac mitochondria extends far beyond that of being merely the 'powerhouse' of the cell. The past decade has witnessed a number of developments in the field of mitochondrial dynamics – a phenomenon in which changes in mitochondrial shape and movement have been demonstrated to impact on cellular physiology and pathology. Mitochondria are dynamic organelles which are able to change their shape by undergoing fusion to generate elongated interconnected mitochondrial networks, and fission to produce discrete fragmented mitochondria. These processes are under the regulation of the mitochondrial fusion and fission proteins, respectively, and are essential for maintaining a healthy mitochondrial network. The cardiac mitochondria, in particular, have garnered much interest due to their unique spatial arrangement in the adult heart, and the multiple roles they play in cell death and survival. It is known that the actions of the mitochondrial fusion and fission proteins extend beyond those of mediating changes in mitochondrial shape – in this regard these pleiotropic roles may impact on their effects in the heart and the vasculature (see Fig. 1). In this article, we review the potential role for the mitochondrial fusion and fission proteins as novel targets for treating cardiovascular disease.

2. Mitochondrial fusion

The fusion of two adjacent mitochondria allows the mixing of intra-mitochondrial proteins and the replacement of damaged

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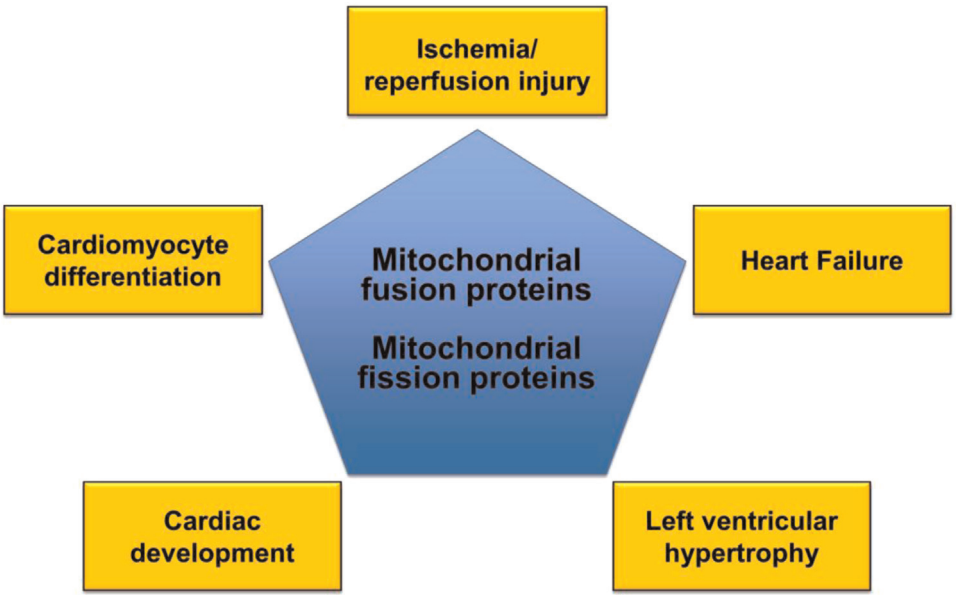

Fig. 1. This scheme provides an overview of the role of the mitochondrial fusion and fission proteins as potential therapeutic targets for treating cardiovascular disease.

mitochondrial DNA (mtDNA) (Legros et al., 2002). In the outer mitochondrial membrane (OMM), Mitofusins 1 (MFN1) and 2 (MFN2) mediate the fusion of the OMM, whereas in the inner mitochondrial membrane (IMM), Optic Atrophy 1 (OPA1), governs the fusion of the IMM (reviewed in Youle and van der Bliek (2012)). The mitochondrial fusion proteins contain a GTPase domain, a transmembrane domain, and a coiled-coil domain. The proteins are anchored to the mitochondrial membrane by the transmembrane domain and it is the coiled-coil domains facing the cytosol that mediate the formation of homotypic (MFN1–MFN1, MFN2–MFN2 and OPA1–OPA1) or heterotypic (MFN1–MFN2) physical connections (Chen et al., 2003). These links bring adjacent mitochondria together and initiate the fusion of the OMM (Koshiba et al., 2004; Chan, 2006), while the formation of OPA1–OPA1 homotypic complexes fuse the IMM.

2.1. *The Mitofusins (MFN1 and MFN2)*

The main role of the Mitofusins is to mediate the fusion of the OMM of adjacent mitochondria. The GTPase activity of the Mitofusins is regulated by guanine nucleotide binding protein-β subunit 2 (Gβ2) (Zhang et al., 2010), and in this regard, MFN1 has been reported to have a higher GTPase activity as compared to that of MFN2 (Ishihara et al., 2004). The pro-fusion effects of MFN1 can be promoted by binding of Gβ2 to MFN1 which decreases its motility and facilitates its clustering at specific foci on the OMM (Zhang et al., 2010). MFN2, however, is regulated by expression levels rather than other post-translational modifications. One such scenario is during mitochondrial biogenesis where PGC1-α and PGC1-β up-regulate MFN2 expression to promote mitochondrial fusion (Zorzano et al., 2009; Liesa et al., 2008). Nevertheless, the ubiquitination of MFN1 and MFN2 promotes the degradation of these proteins allowing unopposed mitochondrial fission during the selective removal of dysfunctional mitochondria by mitophagy (Tanaka et al., 2010; Gegg et al., 2010).

2.1.1. *Pleiotropic non-fusion roles of Mitofusins*

The role of the Mitofusins extends beyond that of mediating mitochondrial fusion of the OMM – this makes the investigation of these proteins in the adult heart quite challenging. Pleiotropic non-fusion actions of the Mitofusins have been mainly described for MFN2 although emerging studies suggest that MFN1 may also have non-fusion effects.

2.1.1.1. MFN2 as a tethering protein. MFN2 has been shown to tether the endoplasmic reticulum (ER) to mitochondria thereby allowing the formation of subcellular calcium (Ca^{2+}) domains in close proximity to the mitochondrial calcium uniporter, and facilitating the transfer of Ca^{2+} signalling from the ER to mitochondria (De Brito and Scorrano, 2008). In the heart, efficient Ca^{2+} transfer from the sarcoplasmic reticulum (SR) to mitochondria is essential to tightly couple the energy requirements for cardiac contractility to mitochondrial energy production (Y. Chen et al., 2012). It has been demonstrated that in mice lacking cardiac-specific MFN2, the SR-mitochondrial tethering is disrupted resulting in impaired Ca^{2+} signalling, diminished mitochondrial respiratory function and a deterioration in left ventricular (LV) systolic function.

2.1.1.2. MFN2 and apoptotic cell death. The interactions between pro-apoptotic proteins such as BAX and BAK which translocate to and permeate the OMM, and the mitochondrial fusion and fission proteins remain to be fully elucidated (Youle and Strasser, 2008). Both BAX and BAK have been demonstrated to co-localise with MFN2 in the OMM (Karbowski et al., 2002; Neuspiel et al., 2005). The binding of BAX to MFN2 has been shown to inhibit its pro-fusion function (Neuspiel et al., 2005). MFN2 may also promote mitochondrial pore formation and decrease stability of the mitochondrial membrane thereby facilitating Drp1-mediated mitochondrial fission (Papanicolaou, Phillippo, et al., 2012). The potential role of non-oligomerised or monomeric BAX and BAK in mitochondrial fusion has recently been evaluated in the context of mitochondrial permeability transition pore (MPTP) opening and necrotic cell death (Whelan et al., 2012). Combined ablation of BAX and BAK was found to promote mitochondrial fragmentation, yet the mitochondria were still shown to be resistant to MPTP opening and necrotic cell death. Interestingly, MFN2-deficient cells (Whelan et al., 2012) also exhibited resistance against MPTP opening, supporting the observation that MFN2 may promote this process together with BAX. This notion is based on the speculation that BAX localisation to the OMM may facilitate the formation of hemifusion-related holes which can be used in the exchange of ions during MPTP opening in the presence of stress. The