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Editorial

Mitofusin function is dependent on the distinct tissue and organ specific roles of mitochondria

The integrity of mitochondrial function is pivotal to cell and organ homeostasis. Emerging evidence is rapidly enhancing our understanding of the myriad of programs controlling mitochondrial health, turnover and repair. These processes include the exclusion of impaired fragments of mitochondria via fission and fusion (mitochondrial dynamics) [1], the recycling of de-energized mitochondrial via mitophagy [2], and the replication or expansion of mitochondria via the mitochondrial biogenesis program [3]. Whether all of these programs are uniformly active and how they are coordinated in different tissues that are either; i) intrinsically rapidly dividing (hemopoietic precursor cells) or not (e.g. the heart and brain); ii) have divergent bioenergetic demands and/or iii) distinct mitochondrial functions are only beginning to be explored. Numerous laboratories have systematically taken on this challenge by focusing on the tissue distinct effects of a family of outer mitochondrial membrane GTPase proteins, i.e. the mitofusins which have been found to play essential regulatory roles in a multitude of mitochondrial homeostatic programs including fusion [4], mitophagy [5] and the interaction between mitochondria and the endoplasmic reticulum [6,7].

As background, two isoforms of mitofusin, namely Mfn-1 and Mfn-2, have been identified in mammalian tissues and in humans, and these isoforms share 63% amino acid homology with common functional domains [8]. The earliest studies showed that these proteins functioned in the initiation of mitochondrial fusion by the tethering of two adjacent mitochondrial outer membranes (recently reviewed in [4]). In this context the mitofusins function as either homo- or heterotypic dimers or in larger complexes. Mfn-1 dominant mitochondria exhibit greater tethering-efficiency than Mfn-2 enriched mitochondria. The genetic ablation of Mfn-1 or Mfn-2 results in embryonic lethality suggesting essential developmental roles for both isoforms [9,10]. Consistent with the greater inter-mitochondrial tethering capacity, the Mfn-1 knockdown MEF cells showed greater disruption in mitochondrial fusion compared to the Mfn-2 null MEF cells [9]. Additional roles for Mfn-2 have begun to emerge. Mfn-2, has recently been implicated in the recycling of cellular content during starvation induced autophagy [11]. Here, Mfn-2 tethers the mitochondrial outer membrane to the endoplasmic reticulum (ER). This facilitates the transfer of phosphatidylserine from the ER to mitochondria, which in turn, is required for phosphatidylethanolamine production employed in autophagosome membrane formation. Another role of the Mfn-2 interaction between mitochondria and ER is to control calcium flux between these two intracellular organelles [6]. The expression pattern of the Mitofusins may also implicate distinct functioning with Mfn-1 being ubiquitously expressed and Mfn-2 enriched in the heart and skeletal muscle [12]. Taken together, these distinct and overlapping roles of the Mitofusins in modulating numerous mitochondrial homeostatic processes, make the study of this family of proteins an attractive system to study mitochondrial functioning in tissues with differing mitochondrial functions.

1. Mfn function in skeletal muscle

Skeletal muscle has a robust regenerative capacity, although is not generally a rapidly dividing organ, and has high levels of both Mitofusin isoforms. The relative roles of these outer mitochondrial membrane proteins have been explored by the Chan laboratory following the post-natal conditional knockdown of each isoform alone or in combination [13]. There appears to be some redundancy in skeletal muscle in that the knockdown of either isoform in isolation does not have a robust phenotype. However, the depletion of both Mfn-1 and Mfn-2 resulted in a stark phenotype with grossly perturbed mitochondria and premature lethality [13]. Prior to the development of physiologic sequelae, the absence of both Mitofusins resulted in the disruption of the fidelity and levels of skeletal muscle mtDNA in these mice. Subsequently, mitochondrial proliferation appears to be a compensatory event. However, the ultimate consequences included mitochondrial respiratory dysfunction, muscle atrophy, severe hypoglycemia, hypothermia and early mortality by 6 to 8 weeks of age. Taken together these data show that mitochondrial fusion component of mitochondrial dynamics is essential for the maintenance of mtDNA quality control and levels. Furthermore, the loss of this homeostatic mitochondrial function in skeletal muscle in the postnatal mouse has robust organ specific and systemic effects. The systemic effects arise in part, due to the central role of skeletal muscle in glucose homeostasis and thermoregulation.

2. The role of Mfn-2 in the heart

At a similar time, the Walsh laboratory began by interrogating the function of these proteins in the heart, an organ which sustains high-bioenergetic demand, is 'terminally-differentiated', with a low rate of mitochondrial dynamic flux. Here, the conditional knockdown of cardiac Mfn-2 resulted in the modest enlargement of mitochondria without a robust effect on basal mitochondrial respiration or cardiac function [14]. The depletion of Mfn-2 did, however, attenuate cardiac cell death in response to ischemia–reperfusion injury and the potential to undergo calcium-dependent mitochondrial permeability transition. Together, these data implicate that Mfn-2 plays a pivotal role in stress-tolerance and in the communication between mitochondria and the sarcoplasmic reticulum in this bioenergetic tissue that has a low to negligent rate of cell division and a proposed low

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rate of mitochondrial dynamics. These data also support the importance of Mfn-2 in the control of intracellular calcium stores in the cardiac response to metabolic stressors.

3. Mfn biology in endothelial cells

In this issue of JMCC the same group studied the effect of both Mitofusin isoforms on endothelial cell biology, a component of the vessel wall with relatively lower energetic demands and a higher rate of cell turnover than the heart [15]. Interestingly, the density of mitochondria is modest in endothelial cells, and here mitochondria are proposed to function predominantly as biological sensors and signaling intermediates as opposed to a primary source of energy production [16,17]. The first intriguing observation in this study, that implicated a role for Mfn biology, was that both isoforms were induced in response to endothelial cell exposure to the angiogenic mitogen vascular endothelial growth factor (VEGF). In contrast to the findings in skeletal muscle described above, the knockdown of either isoform did result in de-energized mitochondria and affected endothelial cell function by impairing VEGF-mediated cellular migration and network formation. In addition, distinct roles for these isoforms were noted in the endothelial cells, where the exclusive reduction in Mfn-2 levels blunted basal and stress-induced reactive oxygen species levels, and in contrast, only the knockdown of Mfn-1 impaired VEGF signal transduction and nitric oxide production. The response to the combined knockdown of both isoforms was not explored in these endothelial cell studies.

4. Mfn-2 in mitochondrial mobility in neuronal tissue

An additional tissue specific role of the Mfn-2 has recently also been delineated in mice and primary dorsal root ganglion neuronal cells [18]. As background, and in contrast to the relatively static position of mitochondria in the heart [19], the distribution of mitochondria down the axonal length is thought to be required for local ATP production and calcium buffering. Mitochondrial transport is regulated in axons by molecular adaptors that mediate the attachment of mitochondria to molecular motors. In this study, the absence of, or mutations in Mfn-2, impaired the regulation of mitochondrial transport and appears to function in part by the disruption of the interaction between Mfn-2 and members of the molecular complex, namely Miro and Milton, which link mitochondria to kinesin motors.

5. Conclusions

Putting all of these studies together illustrates both the broad array of functions of mitochondria in distinct organ and tissue types and highlights the pleiotropic role of the Mitofusin proteins in controlling mitochondrial homeostasis and fitness. Additionally, all of these elegant genetic studies uncover how the manipulation of a single protein/family of proteins can not only dissect out the biological function of the candidate protein/s but also reveal the role of the organelle with which that protein interacts. Further studies in different organ systems will further uncover intriguing roles of these outer mitochondrial tethering proteins on overall mitochondrial and cellular homeostasis. However, an emerging concept from the work to date suggests that Mfn-1 has a 'mito-centric' role and that Mfn-2 plays an important role in the interaction of mitochondria with surrounding organelles and intracellular structures.

Conflict of interest statement

None.

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