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Cardiac-specific research platforms engender novel insights into mitochondrial dynamism

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Abstract

Cardiac myocyte-specific gene manipulation is facilitated by reagents permitting temporal control over transgene expression or gene ablation, and by physiological phenotyping platforms that complement post-mortem cellular and pathological analyses. The ease of creating cardiac-specific gene modified mice may have contributed to genetic mouse models lacking strong underlying mechanistic rationales; this was argued for genetic ablation of mitochondrial dynamics factors in cardiac myocytes that exhibit little evidence for mitochondrial dynamism. Here, I review recent published studies in which experimental *in vivo* manipulation of mitochondrial fusion and fission genes has revealed non-canonical functioning dynamics factors in mitochondrial quality and quantity control. Targeting mitochondrial dynamics proteins in the cardiac system, where mitochondrial dynamism is barely observed, was essential to uncovering novel functioning of these factors in other pathways.

Introduction: being special is not so special

As cardiologists and cardiovascular researchers the concept that ‘the heart is a special case’ can become so deeply engrained in our scientific outlook that it becomes a major factor driving hypothesis development and experimental design, thereby limiting conclusions. Compared to a ‘generic’ cell, adult mammalian cardiac myocytes are atypical in that they are (for all practical purposes) non-replicative/non-regenerative, electrically excitable, and have among the highest basal metabolic activity and mitochondrial density of any cell type. Cardiac myocyte mitochondria do not conform to the classic description as being ‘highly dynamic and interconnected’ [1]. Mitochondria of adult cardiac myocytes are ovoid rather than elongated [2,3••], are static rather than dynamic [4–6], and exist as physically discreet organelles distributed along the long axis of the cell between sarcomeric elements rather than as members integrated into a greater mitochondrial continuum (although there is accumulating evidence that cardiac myocyte mitochondria can communicate between individuals [4] and function as a collective within discrete geographic zones [7]) (Figure 1). Thus, it has become common within the cardiovascular research community, and particularly among those who study mitochondria, to dismiss findings in non-cardiac myocytes as

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Conflict of interest

The authors declare that there is no conflict of interest.

irrelevant to cardiac biology, even if the findings in different cell systems are fully concordant. Moreover, the non-cardiac community is fully aware of the distinguishing features of cardiac myocytes, and sometimes poses ‘the heart is a special case’ argument to negate the potential relevance to non-cardiac systems of primary data originating in cardiac myocyte models [8].

Our experience over the past 5 years has taught us that investigating the unique qualities of cardiac myocyte mitochondria can provide a path toward understanding unanticipated non-canonical functioning of mitochondria in other (and perhaps most) cell types. For example, rather than blindly insisting that cardiac myocyte mitochondria are highly dynamic and undergo frequent cycles of fusion and fission in contrast to observational data, we asked whether highly abundant mitofusin (Mfn) proteins in mouse hearts might function in ways other than morphological mitochondrial remodeling. In exploring this question we uncovered a completely unexpected role for the mitochondrial fusion protein Mfn2 in PINK-Parkin mediated mitophagy signaling [9]. The particulars of this signaling pathway and the general crosstalk between mitochondrial dynamics and mitophagy have also been observed in fibroblasts and neurons [3••,10]. Because phenotypes observed after Mfn2 ablation in cells having ‘normally’ dynamic mitochondria were attributed to the default mechanism of interrupted mitochondrial dynamism, mitochondrial fusion proved to be a confounding variable obscuring a central role for Mfn2 in mitophagy signaling. It required studies of adynamic cardiac myocyte mitochondria to reveal non-fusogenic functioning of this mitochondrial fusion protein in the PINK-Parkin mitophagy pathway.

Hearts and brains; the mitochondrial connection

Notwithstanding that the human heart is the most mitochondria-rich and mitochondria-dependent organ, hereditary human diseases caused by loss-of-function mutations affecting key non-metabolic mitochondrial proteins are notable in that they do not typically affect the heart. Instead, there is an as-yet poorly understood predilection for mitochondrial mutations to provoke chronic neurodegenerative diseases. For example, damaging mutations affecting the mitophagy signaling factors Parkin or PINK1 can cause Parkinson’s disease [11–14], loss-of-function mutations affecting the outer mitochondrial membrane fusion protein Mfn2 can cause Charcot Marie Tooth disease type 2A [15,16], mutations affecting the inner mitochondrial membrane fusion/architecture protein Opa1 can cause dominant optic atrophy [17], and mutations affecting the mitochondrial fission protein Drp1 can cause encephalopathy [18–22]. It is perplexing that heart disease is not a typical feature of any of these syndromes since direct (Mfn1, Mfn2, Drp1) or indirect (Opa1) cardiac myocyte-specific genetic deletion of these factors in mice (excepting PINK1 which has yet to be conditionally ablated in hearts) provoked profound and frequently lethal cardiac phenotypes [3••,9,23–25,26•,27,28,29••].

We asked why hearts are spared in clinical human neurodegenerative diseases caused by damaging mutations of mitochondrial proteins that are essential for normal cardiac functioning in experimental mouse models. Neurons and cardiac myocytes share many characteristics that we posit should make them jointly susceptible to mitochondrial injury: both are excitable cells with a high basal metabolic activity, neither cell type is capable of

proliferation and therefore both are incapable of repairing through regeneration, and the mitochondria of both cell types tend to be arranged as individual organelles rather than in interconnected networks. The one obvious distinction, however, is cell morphology. An adult human cardiac myocyte is ~200–300 μm in length whereas a human sciatic nerve neuron originating in the lumbar spinal cord and terminating in the foot can be up to a meter in length (Figure 1). The orders of magnitude difference in long axis dimension suggests profound dissimilarities in the requirement for and mechanisms by which mitochondria are distributed throughout these two cell types. In this context the key feature underlying susceptibility of neurons to mitochondrial damage may be the requirement for neuronal mitochondrial trafficking over long physical distances (rather than any peculiarities in mitochondrial size, shape, or fission/fusion dynamics). Indeed, small molecule peptidomimetics of previously described minipeptide mitofusin agonists [30•] were recently proven to be remarkably effective at normalizing mitochondrial trafficking in both cultured neurons and mouse sciatic nerves expressing human Charcot Marie Tooth disease Mfn2 mutations [31••] (Figure 2). These results support an approach of using gene manipulation of mitochondrial dynamics proteins in the static mitochondria of *in vivo* adult mouse hearts not only to provide insights into the functioning of these factors in the 'special cases' of normal and diseased hearts, but to uncover previously unrecognized roles for these proteins in other tissues wherein their canonical effects on mitochondrial fusion/fission and trafficking obfuscate parallel functionality.

Mitochondrial dynamism — a matter of balance

Functional interactions between mitochondrial fusion/ fission and quality control pathways occur at both the individual molecular and integrated organelle physiological levels. As an example of dual molecular functioning of a single protein in different pathways, PINK1-mediated phosphorylation of Mfn2 simultaneously converts it from a mitochondrial fusion protein that does not bind Parkin to a non-fusogenic protein that recruits Parkin to outer mitochondrial membranes [3••,9] (Figure 2). Indeed, this process likely contributes to functional sequestration of damaged mitochondria by abrogating their ability to fuse with other mitochondria while targeting them (via the downstream mitophagic effects of Parkin recruited to phospho-Mfn2) for elimination by autophagosomal engulfment and transfer to degradative lysosomes.

The processes of mitochondrial fusion and fission also play integral roles in mitophagic mitochondrial quality control, independent of their specific individual molecular mediators. The central role for mitochondrial fusion and fission in mitophagy was initially described by Shirihai and colleagues [32,33]. Briefly, mitochondria undergo asymmetric fission in a manner that segregates damaged from healthy mitochondrial components, producing two daughter organelles having opposing characteristics: The daughter that received healthy components is 'rejuvenated' and re-joins the functionally productive mitochondrial collective through a combination of fusion with other healthy mitochondria and incorporation of biogenically-derived new parts [34]. The other daughter mitochondrion, which received the damaged parental components, is typically smaller and depolarized, that is, the normal inner mitochondrial membrane electrochemical gradient that drives ATP production has partially or completely dissipated. As a consequence of its depolarization, the

dysfunctional daughter organelle is targeted for mitophagic elimination via the standard PINK-Parkin pathway [35]. This paradigm, in which fission, fusion, and mitophagy are inextricably linked during mitochondrial quality control, has proven to be broadly applicable in *in vitro* systems wherein mitochondrial fusion, fission, and mitophagy are comparatively easy to identify and quantify. However, translating these findings to *in vivo* mammalian systems has proven to be challenging.

Because cardiac myocyte mitochondria do not utilize fission and fusion as a means to structurally modulate mitochondrial networks (because networks do not exist in adult cardiac myocytes), cardiac myocyte-targeted gene manipulation unexpectedly proved to be an effective means of evaluating the *in vivo* functional interactions between these mitochondrial dynamics and mitochondrial quality control independent of the confounding effects of mitochondrial interconnectivity. By employing available floxed allele mice [36,37] in combination with tamoxifen-activated cardiac myocyte-specific Cre mice [38], Moshi Song in our laboratory developed mouse lines in which the initiating factors for either mitochondrial fusion (the two outer membrane tethering and fusion proteins, Mfn1 and Mfn2) or mitochondrial fission (Drp1) could be conditionally ablated specifically in cardiac myocytes of adult (8 week old) mice [26•]. In parallel, Ms. Song developed primary cultured murine embryonic fibroblasts (MEFs) from each floxed mouse line (Mfn1/Mfn2 and Drp1) so that the targeted genes could be ablated in cultured cells using adenoviral Cre. In this manner the *in vivo* consequences on hearts and *in vitro* consequences on cultured MEFs of genetically interrupting mitochondrial fusion and fission could be directly compared. Interrupting mitochondrial fission (Drp1 ablation) evoked a delayed increase in unregulated mitophagy, ultimately producing mitochondropenia (loss of mitochondria). The converse experiment produced the reciprocal result: interrupting mitochondrial fusion (Mfn1/Mfn2 ablation) suppressed mitophagy, which resulted in progressive accumulation of damaged mitochondria [26•] (Figure 3). Abrogating mitochondrial fission and fusion in adult mouse hearts generated opposite, but equally lethal, cardiac phenotypes: Drp1 ablation caused a rapidly progressive dilated cardiomyopathy, whereas combined Mfn1/Mfn2 ablation caused eccentric cardiac hypertrophy; both conditions were uniformly lethal after ~8 weeks. These studies provided the first *in vivo* evidence supporting major pathophysiological importance of functional interactions between mitochondrial fission/fusion and mitochondrial quality control pathways as described *in vitro* in Shirihai's studies [32].

A question raised by the above results was whether it was absolute loss of mitochondrial fusion in Mfn1/Mfn2 null hearts, and fission in Drp1 null hearts, that provoked mitochondrial abnormalities and cardiac disease. The counter hypothesis posits that relative hyperactivity of Drp1-mediated fission in Mfn1/Mfn2 null hearts, and of Mfn1/Mfn2-mediated fusion in Drp1 null hearts, provoked mitochondrial and myocardial abnormalities. Ms. Song reasoned that simultaneous combined interruption of fission and fusion would exacerbate cardiac disease if the former hypothesis were correct, but would ameliorate cardiac disease if dynamic imbalance rather than absolute loss of fission or fusion was the key damaging feature. Accordingly, she crossed the fusion-defective Mfn1/Mfn2 and fission-defective Drp1 floxed allele mice to generate mice with hearts in which simultaneous defects in both mitochondrial fusion and fission (which she called 'adynamic mitochondria') could be genetically induced [29••]. Compared to the parent fusion-defective or fission-

defective mice, mice with adynamic cardiac myocyte mitochondria lived 3-times longer and exhibited a third distinct phenotype: concentric hypertrophy that failed (i.e. developed severely reduced ejection performance) without transitioning through the typical stage of cardiac dilatation and wall thinning (Figure 3). As in the parent lines, the cardiac pathologies could be mechanistically linked to abnormalities in mitophagy. In adynamic mitochondria of Mfn1/Mfn2/Drp1 hearts, intrinsic mitophagy interruption prevented mitochondropenia seen when fission alone was interrupted, thus preempting the dilated cardiomyopathy provoked by hypermitophagic mitochondrial insufficiency. In the absence of the typical Shirihai mechanism for fission-mediated triage of healthy versus damaged mitochondrial components [32], the mitochondrial collective increased in both overall abundance and organellar senescence, that is, there was evidence of increased mitochondrial 'wear and tear' [29••]. The degree of adynamic mitochondrial dysfunction and proteotoxic stress in Mfn1/Mfn2/Drp1 null mouse hearts should have been sufficient to trigger normal mitophagic quality control mechanisms, but it could not because Mfn2 is a critical mediator of the PINK1-Parkin pathway. Nevertheless, compensatory mitochondrial quality control mechanisms were sufficient to prevent cytotoxicity. Indeed, cardiac hypertrophy and dysfunction paralleled the increase in mitochondrial mass rather than mitochondrial dysfunction. These results point to the mitochondrial dynamism/mitophagy interactome as a key regulator not only of mitochondrial quality, but also of mitochondrial quantity, in the *in vivo* mammalian heart. The importance of mitophagic mitochondrial quantity control in other tissues, and the nature of the regulatory mechanisms orchestrating biogenic and mitophagic regulation of mitochondrial mass, remains unclear at this time.

Summary

Just a few years ago mitochondrial dynamics (fission and fusion), mitochondrial biogenesis (a form of quantity control), and mitophagic mitochondrial quality control were considered to be largely separate and mechanistically distinct processes. This has been demonstrated to not be the case. Rather, the three processes function within a greater 'interactome' in which physiological, pathological, or genetic perturbations of one are reflected by co-regulation or counter-regulation of the other two. As reviewed above, the unique attributes of the heart have proven invaluable to discovering these functional interactions and to demonstrating their relevance to working organ systems in *in vivo* mammalian systems.

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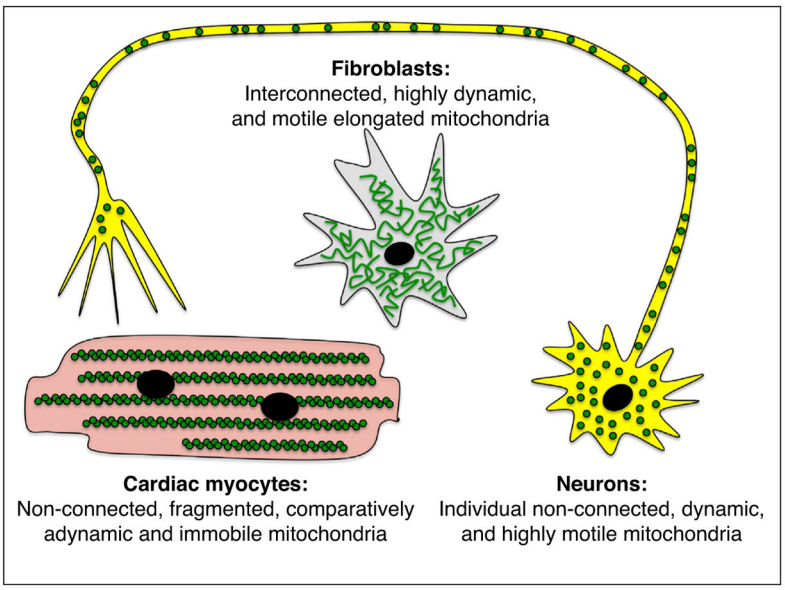

Figure 1.

Comparison of mitochondrial features in fibroblasts, cardiac myocytes, and neurons. Mitochondria (green) arrangement, morphology, and dynamism in three prototypical cell types wherein mitochondrial function is of particular interest.

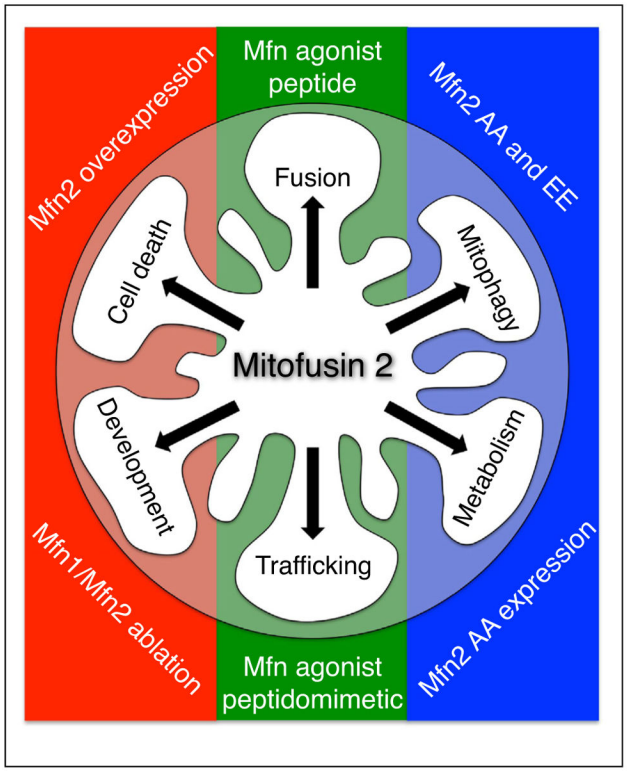

Figure 2.

Different roles played by Mfn2 in mitochondrial fusion, motility, and mitophagy and how they have been experimentally modulated. Mfn2 roles in cell death and cardiac development are not reviewed here and are included for completeness. Modulation of mitochondrial fusion and trafficking by Mfn agonist peptides and small molecule peptidomimetics is from Refs. [30•,31••]. Regulation of mitophagy and perinatal cardiac metabolic transitions by Mfn2 mutants with modified T111 and S442 PINK1 phosphorylation sites (Mfn2 AA and EE) is described in Refs. [3••,9].

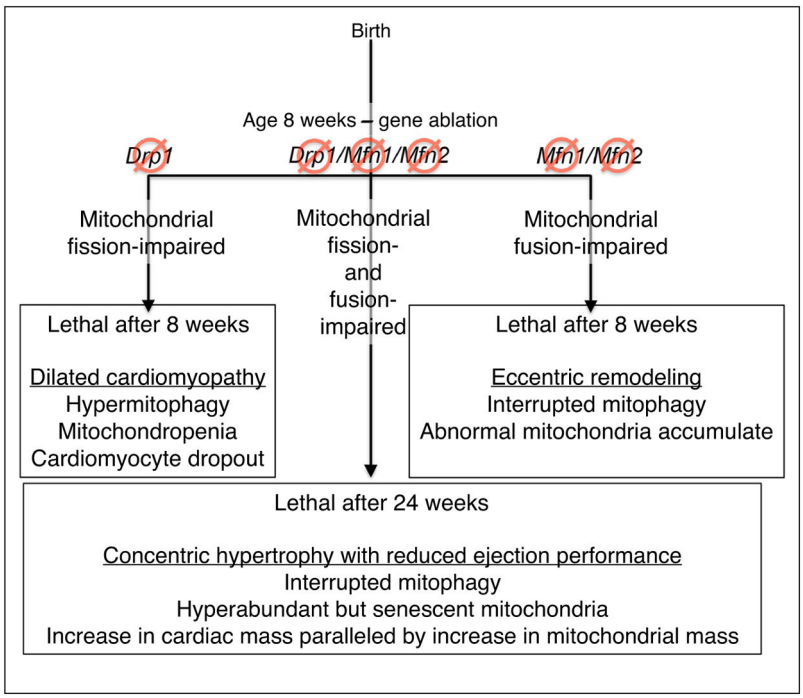

Figure 3.

Interactions between mitochondrial dynamism and mitophagy in mitochondrial quality and quantity control pathways, as defined by studies of *in vivo* mouse hearts. This diagram summarizes the cardiac and mitochondrial phenotypes described in Refs. [26•,29••].