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Review

Mitochondrial dynamics in heart disease ☆

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ABSTRACT

Mitochondrial fission and fusion have been observed, and their importance revealed, in almost every tissue and cell type except adult cardiac myocytes. As each human heart is uniquely dependent upon mitochondria to generate massive amounts of ATP that fuel its approximately 38 million contractions per year, it seems odd that cardiac myocytes are the sole exception to the general rule that mitochondrial dynamism is important to function. Here, I briefly review the mechanisms for mitochondrial fusion and fission and examine current data that dispel the previous notion that mitochondrial fusion is dispensable in the heart. Rare and generally overlooked examples of cardiomyopathies linked either to naturally-occurring mutations or to experimentally-induced mutagenesis of mitochondrial fusion/fission genes are described. New findings from genetically targeted *Drosophila* and mouse models wherein mitochondrial fusion deficiency has specifically been induced in cardiac myocytes are discussed. This article is part of a Special Issue entitled: Mitochondrial dynamics and physiology.

1. Introduction

Cardiologists like to point out that the heart is the hardest working organ in the human body. It is widely reported that the human heart consumes 30 kg of ATP per day fueling basal metabolism and normal contraction that is essential to sustaining systemic and pulmonary blood pressure [1]. Obviously, a ~300 g heart that daily consumes 100 times its weight in ATP does not do so by relying upon stored reserves, but must constantly be generating it. Almost all ATP is produced in cardiomyocyte mitochondria, with trivial amounts created in the cytosol. Accordingly, ventricular myocardium is literally packed full of mitochondria, which account for ~35% of cardiomyocyte volume [2]. There are more mitochondria in mammalian myocardium than there are individual muscle sarcomeres (~2:1) (Fig. 1).

Mitochondrial ATP production is tightly regulated to meet varying metabolic demands resulting from minute-by-minute (or Beat-to-beat) changes in cardiac work. While the components of oxidative phosphorylation and the electron transport chain are fully understood, the molecular details of their regulatory pathways remain controversial. Two major mechanisms have been proposed: Regulation by ADP and inorganic phosphate (Pi) that are the products of ATP hydrolysis, and regulation by cytosolic calcium ($[Ca^{2+}]_c$) that is released from the SR and sensed by the mitochondria in response to stimuli for increased work. The former classical hypothesis [3] has been disputed by Balaban and colleagues who found that large changes in cardiac work and ATP consumption are not associated with measurable changes in ADP/Pi levels [4,5], while the latter hypothesis has gained credence from elegant studies of O'Rourke and coworkers [6,7]. It seems likely that modulatory functions may exist for both ATP/ADP/Pi and $[Ca^{2+}]_c$, the former playing a greater role regulating mitochondrial oxidative phosphorylation while the latter mainly affects Krebs cycle dehydrogenases [8].

The unique bioenergetic requirements of the heart not only dictate that it generate and maintain the largest proportional density of mitochondria of any organ in the body, but that the mitochondria are organized throughout the cardiac myocyte in a highly structured and stable manner. As their names suggests, repeating ribbon-like clusters of interfibrillar mitochondria run between myofibrils arranged parallel to the long axis of the cardiomyocyte. This enforced proximity of mitochondria to sarcomeres throughout the cardiomyocyte provides for a ready and continuous supply of ATP to all components of actin–myosin contractile machinery. Similarly, deep T-tubular invaginations of the cardiomyocyte plasma membrane (sarcolemma) inter-digitate at close intervals into the myofibrillar elements and mitochondrial clusters. Synchronization of calcium entry throughout an electrically depolarized cardiomyocyte is critical for harmoniously initiating and terminating normal excitation–contraction coupling [9]. The T-tubules facilitate coordinated calcium (Ca^{2+}) import and export throughout all parts of the cardiomyocyte simultaneously.

A third cellular organelle structure, the sarcoplasmic reticulum, likewise forms a continuous network that surrounds and permeates myofibrils and is intimately associated with mitochondrial clusters. Sarcoplasmic reticulum (SR) is the primary calcium storage and release organelle for cardiomyocytes, and the source of the vast majority of the

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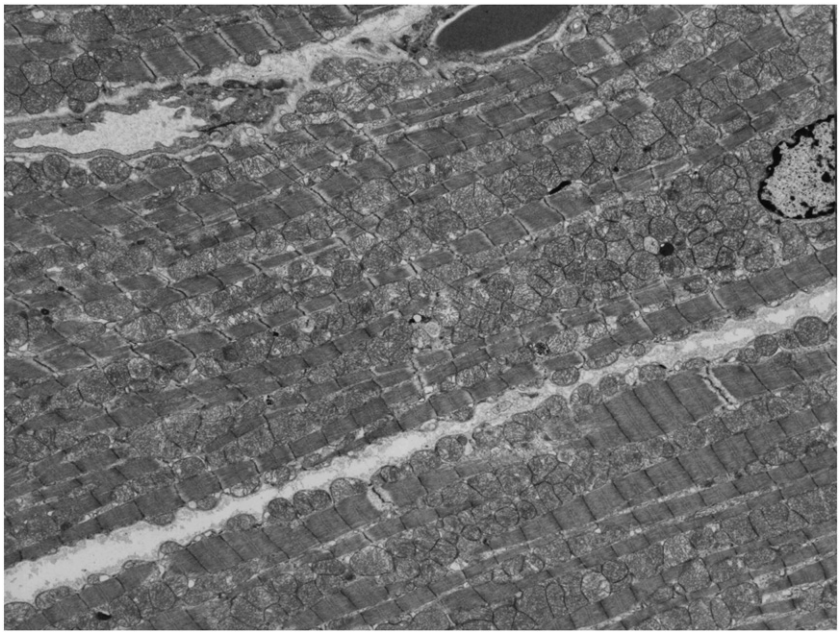

Fig. 1. *Subcellular arrangement of mitochondria in normal adult cardiomyocytes.* Transmission electron micrograph of normal 8 week old mouse myocardium. Note lanes of interfibrillar mitochondria running between individual myofibrils and cluster of mitochondria surrounding nucleus (bisected on right margin). The "sardines in a can" arrangement appears to enforce inter-organelle contact and does not permit meaningful intra-cellular mitochondrial transport.

free cytosolic Ca^{2+} that drives sarcomeric contraction [9]. SR Ca^{2+} release is a passive process. In contrast, large amounts of ATP are required to fuel SR Ca^{2+} reuptake via the SR Ca^{2+} ATPase (SERCA) that, together with a smaller amount of cardiomyocyte calcium export through the Na/Ca exchanger (NCX; [10]) and plasmalemmal Ca^{2+} ATPase (PMCA; [11,12]), terminates contraction [13]. Physical proximity between cardiomyocyte mitochondria and SR is enforced in the same way that proximity between individual sardines is assured in a can, they are confined in groups within a highly ordered compacted structure. This arrangement ensures an ample supply of mitochondrial ATP to power SR calcium reuptake pumps and may provide a means whereby mitochondria sense increased SR calcium release that presages increased cardiac contraction. Mitochondrial sensing of cytosolic Ca^{2+} released from the SR stimulates an anticipatory increase in ATP production to fuel the impending greater workload, thus preventing the energy deficit that would otherwise occur after acutely increased ATP consumption [14].

The paradigm described above is consistent with a static cardiomyocyte subcellular architecture in which organelle interactions are dictated by physical proximity, the "sardines in a can" model (Fig. 1). Sarcomeric myofilaments run the length of cardiac myocytes with ribbons of mitochondria interspersed between, and the SR exists as an intercalated network surrounding myofilaments and mitochondria like fish net stockings. This model contrasts with that described for neurons, in which individual mitochondria are widely dispersed and are transported from the cell body along the axons to the synapse, and perhaps back again [15]. During the course of their axonal journeys, neuronal mitochondria transiently link to and fuse with other mitochondria in cycles of tethering, fusion, and fission that promote organelle regeneration through exchange of internal mitochondrial contents [16]. Indeed, the molecular and biophysical mechanisms for mitochondrial fusion and fission have been elucidated in detail in neurons, fibroblasts, and other cell types, as described in other articles within this compendium. Until recently however (when results of studies that manipulated mitochondrial fusion proteins in mouse and fruit fly hearts suggested otherwise, vide infra), it was generally assumed that the unique subcellular architecture and apparent absence of mitochondrial mobility in adult cardiac myocytes either precluded, or obviated the need for, mitochondrial tethering, fusion and fission [17]. Here, we review new findings that have altered the perception that cardiac mitochondria are static, exploring the evidence for and roles of mitochondrial dynamics in normal and diseased hearts.

2. The machinery of mitochondrial fusion/fission

The striking morphometric diversity of mitochondria has been recognized for over a century. Indeed the word "mitochondrion" is widely reported to refer to this morphological heterogeneity as it is derived from the Greek words "mitos" (thread) and "khondros" (grain or granule), which would seem to represent different observed organelle shapes [18]. However, in medical parlance "chondros" primarily refers to cartilage, and the term "mitochondria" was first used in 1898 by Carl Benda who postulated that the many microscopic intracellular structures he detected by light microscopy acted like posts or pillars to support and maintain the cell's overall size and shape. Accordingly, he called these presumed cytoskeletal structures mitochondria, or "threads of cartilage". Subsequent advances in optics and biochemistry and the development of live-cell microscopy led to the realization that mitochondria were cellular power supplies, correcting this functional misconception. In 1914 Lewis and Lewis discovered mitochondrial dynamism, describing cycles of mitochondrial fusion and fission in various cultured chick embryo tissues [19]: "We find in the living (cells) that (mitochondria) can be seen to fuse together into rods or chains, and these to elongate into threads, which in turn anastomose with each other and may unite into a complicated network, which in turn may again break down into threads, rods, loops and rings." Mitochondrial mobility, fusion and fission have since been observed in almost every species (from yeast to human) and cell type *except adult cardiac myocytes*. Mitochondrial fission is seen in neonatal cardiac myocytes and various immortalized cardiomyocyte-like cells undergoing apoptosis [20–24]. However, cultured neonatal cardiomyocytes have a much less structured internal architecture than adult cardiomyocytes, entirely unlike the highly organized "sardine can" design described above. Indeed, there are no published direct observations of mitochondrial fusion or fission in *normal* adult cardiac myocytes. Specific attempts to detect mitochondrial fusion in adult cardiomyocytes using live-cell