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MEDIATORS, MECHANISMS, AND PATHWAYS IN TISSUE INJURY (B ROTHERMEL, SECTION EDITOR)

Mitochondria, Myocardial Remodeling, and Cardiovascular Disease

Hugo E. Verdejo · Andrea del Campo · Rodrigo Troncoso · Tomás Gutierrez · Barbra Toro · Clara Quiroga · Zully Pedrozo · Juan Pablo Munoz · Lorena Garcia · Pablo F. Castro · Sergio Lavandero

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Abstract The process of muscle remodeling lies at the core of most cardiovascular diseases. Cardiac adaptation to pressure or volume overload is associated with a complex molecular change in cardiomyocytes which leads to anatomic remodeling of the heart muscle. Although adaptive at its beginnings, the sustained cardiac hypertrophic remodeling almost unavoidably ends in progressive muscle dysfunction, heart failure and ultimately death. One of the features of cardiac remodeling is a progressive impairment in mitochondrial function. The heart has the highest oxygen uptake in the human body and accordingly it has a large number of mitochondria, which form a complex network under constant remodeling in order to sustain the high metabolic rate of cardiac cells and serve as Ca^{2+} buffers acting together with the endoplasmic reticulum (ER). However, this high dependence on mitochondrial metabolism has its costs: when oxygen supply is threatened, high leak of electrons from the electron transport chain leads to oxidative stress and mitochondrial failure. These three aspects of mitochondrial function (Reactive oxygen species signaling, Ca^{2+} handling and mitochondrial dynamics) are critical for normal muscle homeostasis. In this article, we will review the latest evidence linking mitochondrial morphology and function with the process of myocardial remodeling and cardiovascular disease.

Keywords Hypertension · Mitochondria · Cardiomyocyte · Oxidative stress · Mitochondrial dynamics · Bioenergetics · Cardiovascular disease · Cardiac remodeling · Cardiac hypertrophy · Calcium · Mitochondrial morphology · Mitochondrial biogenesis · Heart failure · Mitochondrial fusion · Mitochondrial fission

H. E. Verdejo · A. del Campo · R. Troncoso · T. Gutierrez · B. Toro · C. Quiroga · Z. Pedrozo · L. Garcia · S. Lavandero (✉)
Centro Estudios Moleculares de la Célula,
Facultad Ciencias Químicas y Farmacéuticas/Facultad de Medicina, Universidad de Chile,
Olivos 1007,
Santiago 8380492, Chile
e-mail: slavander@uchile.cl

H. E. Verdejo · P. F. Castro
Division de Enfermedades Cardiovasculares. Facultad de Medicina, Pontificia Universidad Católica de Chile,
Santiago, Chile

J. P. Munoz
Institute for Research in Biomedicine,
Barcelona 08028, Spain

S. Lavandero
Department of Internal Medicine (Cardiology),
University of Texas Southwestern Medical Center,
Dallas, Texas 75235, USA

Introduction

Cardiovascular disease is a growing health concern worldwide. Heart failure (HF), the common final stage of most cardiovascular diseases, shows a steadily growing prevalence and constitutes a leading cause of death in most of the occidental countries [1]. A core process linking cardiovascular diseases such as hypertension, coronary artery disease and valvular disease to HF is the abnormal remodeling of heart muscle in response to different noxas. Although initially adaptive, cardiomyocyte response to pressure or volume overload is associated with deep molecular changes leading to fetal gene expression, impaired contractile function, abnormal vascularization, altered extracellular matrix composition, fibrosis and profound metabolic abnormalities which almost unavoidably end in progressive HF [2, 3].

Because of the significant economic burden associated with HF, interventions to stop or revert pathological remodeling appear as attractive targets to delay disease progression. Current therapy in HF is aimed to avoid cardiac remodeling via neurohumoral blockade; however, despite the proven beneficial effects of drugs acting on the renin-angiotensin-aldosterone system (i.e. angiotensin converting enzyme inhibitors, AT1 receptor antagonists or aldosterone receptor antagonists) or in the adrenergic system (i.e. beta-adrenergic receptor blockers), mortality and morbidity rates associated with HF remain high, thus showing the need for novel approaches to treat the disease. An emerging therapeutic target is the metabolic derangement, which characterizes HF. In fact, cardiac tissue depends largely on mitochondrial metabolism in order to sustain its high energetic demands. The failing cardiomyocyte has been characterized as an "engine out of fuel" [3]. This energetic impairment is associated with abnormal mitochondrial dynamics, increased oxidative stress and abnormal Ca^{2+} handling [4] which seems to play a critical role on the myocardial remodeling process leading to HF. In this article we will review the latest evidence linking abnormal mitochondrial morphology and function with myocardial remodeling, emphasizing new emerging strategies to avoid HF development and progression.

Mitochondria, Oxidative Stress, and Muscle Remodeling

Reactive oxygen species (ROS) have a dual role in cell signaling. A controlled production of ROS acts as a secondary messenger amplifying signals that are crucial for normal cell function. In contrast, an overt imbalance between ROS production and the cell antioxidant defense systems leads to a breakage from normal homeostasis (oxidative stress) closely related to a wide range of cardiac diseases.

Within the cardiovascular system there are two major sources of ROS: cytosolic enzymes, such as nicotinamide adenine dinucleotide phosphate (NADPH) oxidase and xanthine oxidase, and mitochondria. While cytoplasmic ROS are usually associated with signaling, mitochondrial ROS are primarily a byproduct of mitochondria's role as the major site of oxygen consumption in the cell. During cardiac remodeling and heart failure, both cytosolic and mitochondrial ROS becomes deregulated leading to oxidative damage, mitochondrial dysfunction and ultimately cell death.

It is well established that ROS play a role in myocardium remodeling and progression to heart failure [5], although their effect likely varies depending on ROS type and concentration. Under physiological conditions, mitochondria are responsible for almost all superoxide production in cardiomyocytes; however, during hypertrophy, cytosolic sources such as NADPH oxidase also contribute to increased oxidative stress [6]. In a cardiomyocyte model, Kwon et al. demonstrated that different concentrations of ROS could differentially activate pathways to induce hypertrophy or apoptosis: low ROS concentrations promoted increased survival and hypertrophy through extracellular signal-regulated kinase 1/2 (ERK1/2) activation, while higher concentrations activated stress kinases like c-Jun N-terminal kinase (JNK) and p38-mitogen activated protein kinase (MAPK) [7]. Activation of JNK may link the hypertrophy and mitochondrial dysfunction seen in heart failure; in fact, JNK activation promotes not only cardiomyocyte hypertrophy but also the activation of autophagy through Bcl-2 and nineteen-KDa interacting protein-3 (BNIP3), which ultimately leads to apoptosis and mitochondrial selective autophagy (mitophagy) [8•, 9]. In an intriguing paper, Vacek et al. showed that increased mitophagy may lead to metalloproteinase activation, a key element in cardiovascular remodeling as extracellular matrix degradation leads to increased collagen deposit and impaired cardiomyocyte coupling [10].

Interestingly, the activation of ROS-dependent pathways seems to be characteristic of pathological hypertrophy [11]. Physiological hypertrophy, as seen in high-trained athletes or pregnancy, appears to depend on different signaling pathways such as insulin-like growth factor-1 (IGF-1)/protein kinase Akt and the induction of peroxisome proliferator activator γ coactivator 1α (PGC-1α) leading to increased mitochondrial biogenesis. In contrast, there is a marked reduction in PGC-1α/estrogen-related receptor α (EERα) seen in pathological hypertrophy [12].

Mitochondria have developed specific strategies to avoid ROS induced damage. One of the most interesting is associated with deacetylase Sirtuin 3 (Sirt3), which resides in the mitochondrial membrane and is closely related to redox environment regulation. Sirt3 modifies ROS production both directly, regulating mitochondrial superoxide dismutase (SOD) and isocitrate dehydrogenase (IDH), and indirectly, regulating mitochondrial electron transport chain (mETC) activity, lipid processing and inhibiting mitochondrial permeability transition pore (MPTP) opening [13]. In fact, cardiac hypertrophy enhances Sirt3 expression. Furthermore, Sirt3 knock-out animals subjected to the same stimuli displayed an exacerbated hypertrophic response, suggesting that augmented Sirt3 levels are a compensatory response [14]. Another protein likely involved in maintaining mitochondrial function in the face of increased oxidative stress is the PTEN-induced kinase (PINK). This protein, usually associated with mitophagy, is markedly decreased in advanced stages of heart failure. PINK knock-out mice display spontaneous cardiac hypertrophy, increased cardiomyocyte oxidative stress, impaired mitochondrial function and increased myocyte apoptosis [15].

The relationship between cardiac remodeling and hypertrophy is reciprocal. Mitochondria are not only the main source of ROS in the cardiomyocyte, they are also one of

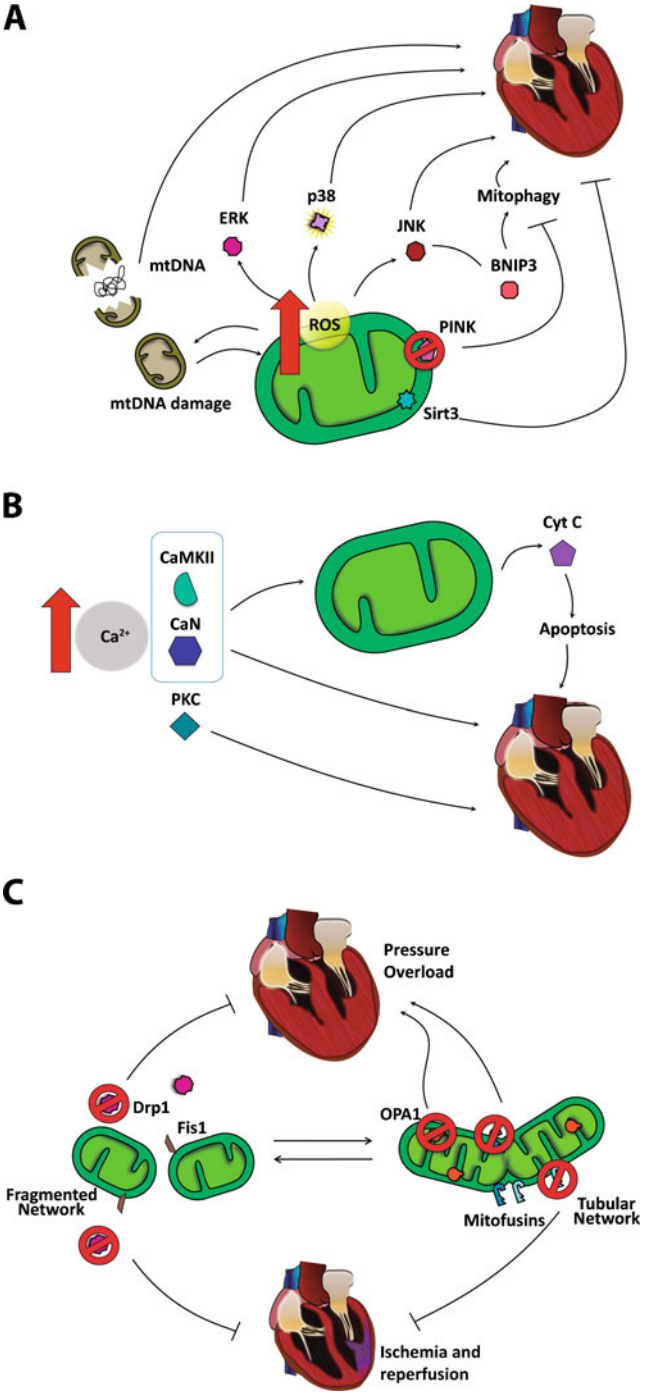

Fig. 1 **a.** Oxidative stress and cardiac remodeling. An increase in mitochondrial reactive oxygen species (ROS) promotes the activation of the mitogen-activated protein kinases ERK, p38 and JNK inducing cardiac hypertrophy. It has recently shown that JNK can activate mitophagy, giving another pathway to promote cardiac failure through BNIP3. Other internal mitochondrial proteins can also regulate these pathways; both PINK and Sirt3 have a protective role against hypertrophy. Moreover the accumulation of ROS inside mitochondria induces mtDNA damage and impairs mitochondrial electron transport chain, increasing ROS production which ultimately leads to a vicious circle inducing further damage. Recently it has been demonstrated that mtDNA itself released from damaged organelles may be responsible of myocardial damage by activation of the innate immune response. **b.** Ca^{2+} signaling and cardiac remodeling. Cytoplasmic Ca^{2+} rise activates the Ca^{2+} -dependent proteins CAMKII, calcineurin (CaN) and protein kinase C (PKC), which in turn induces a characteristic genetic program involved on cardiac hypertrophy development. Also, the activation of CAMKII and CaN promotes mitochondrial fission and MPTP opening; the release of cytochrome c activates cardiomyocyte apoptosis, further contributing to the remodeling process. **c.** Mitochondrial dynamics and cardiac remodeling. The participation of mitochondrial dynamics on remodeling seems to depend on the nature of the injury. In pressure overload models, a decrease in Mfn2 or Opa1 promotes cardiac hypertrophy. Paradoxically, Mfn2 knock down improves the functional recovery after myocardial ischemia/reperfusion. A decrease in mitochondrial fission - via a dominant negative form of Drp1 or pharmacological inhibitors such as Mdivi - decrease cardiac remodeling irrespective of the mechanism (pressure overload or ischemia/reperfusion)

the main targets of oxidative damage. Mitochondrial DNA (mtDNA) is particularly prone to oxidative damage due to its lack of histones and the high levels of ROS generation in the organelle matrix [16]. This oxidative damage may also affect critical steps within the Krebs cycle and also mtDNA polymerase γ, slowing mtDNA replication and eventually leading to inhibition of oxidative phosphorylation [17]. As mtDNA encodes proteins involved in complexes I and III of the mETC, a vicious circle is established leading to progressive mitochondrial dysfunction, as seen in advanced stages of heart failure [18]. The importance of mtDNA has been further supported by the recent discovery that impaired autophagy of mitochondrial DNA released from damaged mitochondria may play a role in the development of the inflammatory response that accompanies certain forms of myocarditis and heart failure [19]. The participation of mitochondrial ROS in cardiac remodeling is summarized in Fig. 1a.

Considering the involvement of mitochondrial ROS in cardiac hypertrophy and remodeling, several investigators have targeted mitochondrial ROS as an approach to preventing cardiac failure. Dai et al. recently demonstrated that mitochondrial-targeted catalase partially protected the heart from failure induced by transverse aortic constriction and consistently attenuated mitochondrial proteome remodeling [20•]. These findings were perfectly mimicked by the mitochondrial-targeted antioxidant SS-31, but not by a non-specific antioxidant such as N-acetylcysteine, reinforcing the concept that mitochondrial ROS are causative in the development of heart failure [21].

Mitochondrial Ca^{2+} Handling in Muscle Remodeling and Cardiovascular Disease

The major function of the heart is to pump blood throughout the circulatory system providing oxygen and nutrients to all

tissues and removing unwanted metabolites. This pumping activity requires essential beat-to-beat rhythmic oscillations in cytosolic Ca^{2+} of individual cardiomyocytes, that drives changes in myofilament interactions promoting contraction and cell shortening [22]. However, in the last two decades a new understanding of the role of Ca^{2+} in programming reactive hypertrophic signaling has emerged. Ca^{2+} is stored mainly in the sarcoplasmic reticulum (SR), which generates Ca^{2+} signals through controlled release of stored Ca^{2+} in to the cytoplasm. In this particular function, two Ca^{2+} channels stand out, the inositol 1,4,5-triphosphate receptor (IP_3R) and the ryanodine receptor (RyR). Following a release from the SR to the cytoplasm, Ca^{2+} is swiftly pumped back by the action of the sarco/endoplasmic reticulum Ca^{2+} ATPase (SERCA), thus maintaining low cytoplasmic concentrations and preventing the depletion of SR Ca^{2+} [22].

Diverse signaling proteins activated by an increase in cytosolic Ca^{2+} have been associated with the development of cardiac hypertrophy, such as calcineurin (CaN), calmodulin-dependent protein kinase (CAMKII) and protein kinase C (PKC). For a more comprehensive review see references [23•, 24•, 25•]. Notably, these proteins are also associated with mitochondrial-dependent cell death. Cardiomyocytes expose to isoproterenol the pro-apoptotic protein Bad dephosphorylate, which then translocates to mitochondria to promote cell death. CaN inhibitors, such as FK506 and cyclosporine, inhibit dephosphorylating of Bad and increase cardiomyocyte survival [26]. In ischemic/reperfusion injury, CAMKII-dependent phosphorylation of phospholamban triggers mitochondria-dependent cell death. The use of KN93 (a CAMKII inhibitor) reduces the release of cytochrome c from mitochondria, mitochondria swelling and lactic dehydrogenase (LDH) release from the cell [27]. On the other hand, post-conditioning of cardiomyocytes protects from cell death through a PKC-ξ, interaction with a Ca^{2+} sensing receptor, that inhibits the SR-dependent increase in cytoplasmic Ca^{2+} and mitochondrial Ca^{2+} overload [28]. The main pathways connecting Ca^{2+} handling and muscle remodeling are illustrated in Fig. 1b.

These observations have fostered an interest in mitochondrial Ca^{2+} handling as a therapeutic target in cardiovascular disease. For example, mitochondria from diabetic hearts have an increased sensitivity to MPTP opening in response to ischemic/reperfusion injury compared to mitochondria from non-diabetic hearts. Blocking the Ca^{2+} influx with the mitochondrial Ca^{2+} uniporter blocker minocycline or reducing ROS levels with the mitochondrial-targeted peptide MTP-131 reduces infarct size in both normal and diabetic hearts [29] demonstrating the importance of mitochondrial Ca^{2+} in this process.

Mitochondria themselves are important targets of Ca^{2+} signaling. Once in the mitochondrial matrix, Ca^{2+} has several mechanisms through which it can regulate mitochondrial metabolism. It was shown several decades ago that Ca^{2+} directly activates pyruvate dehydrogenase phosphatase and three Krebs cycle dehydrogenases [30]. Ca^{2+} also increases activity of the F_1/F_0 ATPase [31] and the ATP/ADP carrier [32]. Thus, mitochondrial Ca^{2+} is essential for cell bioenergetics and a raise in mitochondrial Ca^{2+} concentration can stimulate Krebs cycle activity, increasing NADH levels leading to an increase in ATP synthesis [33•, 34].

Mitochondrial Ca^{2+} uptake is a key determinant for the regulation of mitochondrial metabolism by this ion. Ca^{2+} entrance to the mitochondria is mainly sustained by the mitochondrial Ca^{2+} uniporter (mCU), whose molecular identity has been recently discovered [35]. mCU is a highly selective Ca^{2+} channel, but has a low affinity for Ca^{2+} [36]. As a result, a high concentration of cytosolic Ca^{2+} in the proximity of mitochondria must occur to induce Ca^{2+} entry. To solve this, mitochondria are strategically localized in high Ca^{2+} concentration micro domains near the Ca^{2+} release channels within ER [37, 38]. The close contact formed between ER and mitochondria is regulated by a great variety of proteins located in the interface of the two organelles, including IP_3R, RyR, SERCA and mitofusin-2 (Mfn-2) [39]. The evidence for this coupling in cardiomyocytes is demonstrated by the difficulty of isolating purified cardiac mitochondria free from associated SR vesicles, suggesting a direct physical coupling. These SR particles can also transfer Ca^{2+} to the mitochondria and activate oxidative metabolism [40]. On the other hand, the main mechanism for efflux of mitochondrial Ca^{2+} in cardiomyocytes is a Ca^{2+}/Na^{+} exchanger, which extrudes mitochondrial Ca^{2+} in exchange for Na^{+} [41].

In the heart, where the energy demand is constant, the fine and effective regulation of mitochondrial metabolism is of utmost importance. Work done in neonatal and adult cardiomyocytes have shown that mitochondrial Ca^{2+} levels increase in a beat-to-beat fashion, mirroring cytoplasmic Ca^{2+} levels [42, 43]. Interestingly, in beating adult cardiomyocytes, cytoplasmic and mitochondrial ATP levels remain constant even after an increase in workload, suggesting a tight coupling between energy demand and production. In response to an abrupt stimulation from rest, cardiomyocytes will show a drop in mitochondrial ATP, followed by an increase over basal levels. This reduction in mitochondrial ATP levels is shadowed by an increase in mitochondrial Ca^{2+} [43]. Similar results have been obtained measuring changes in NADH levels in adult rat cardiomyocytes [41]. During increased workload, mitochondrial Ca^{2+} levels are elevated, while NADH levels remains unaltered. However, if Ca^{2+} entry to the mitochondria is blocked using mCU inhibitors or if Ca^{2+} extrusion from the mitochondria is enhanced through the mitochondrial Ca^{2+}/Na^{+} exchanger by increasing cytoplasmic Na^{+} concentration, mitochondria cannot load Ca^{2+} efficiently in response to the increased workload, and NADH levels fall evidencing an energetically compromised cell [41]. Together, these results suggest that Ca^{2+} participates in the fine regulation of mitochondrial metabolism and ATP synthesis.

There are several reports showing that mitochondrial metabolism is altered in heart failure [44, 45]. Interestingly, cardiomyocytes from failing hearts also show a reduction in mitochondrial Ca^{2+} increases after electrical or adrenergic stimulation compared to the response of normal cardiomyocytes, suggesting that the reduction in mitochondrial metabolism may be due to a loss in mitochondrial Ca^{2+} [46]. Furthermore, in failing hearts there are reported important alterations in several Ca^{2+} channels and pumps controlling cytoplasmic Ca^{2+} handling that could explain the reduction in Ca^{2+} influx to the mitochondria [22]. Liu and O´Rourke showed that promoting the accumulation of mitochondrial Ca^{2+} via the inhibition of the Ca^{2+}/Na^{+} exchanger prevented the reduction in mitochondrial metabolism in failing hearts [47]. Thus, the recovery of proper Ca^{2+} handling in mitochondria of failing hearts emerges as an option to prevent the detrimental effects of this condition. In this regard, IGF-1 has been shown to induce mitochondrial Ca^{2+} uptake and mitochondrial respiration and prevent a fall in ATP in nutritionally stressed cardiomyocytes, reducing cell death [48]. Also, Zhang et al, demonstrated a beneficial role for cardiac-specific overexpression of IGF-1 in attenuating or preventing the contractile and metabolic dysfunction induced by high-fat diet [49]. It remains to be determined if targeting Ca^{2+}-dependent mitochondrial function is therapeutically beneficial in the clinical setting of cardiovascular diseases.

Mitochondrial Dynamics and Cardiovascular Disease

The traditional concept of mitochondria as static, isolated organelles has been challenged in recent decades as the mechanisms regulating mitochondrial function have been discovered. Nowadays, we understand mitochondria as a network under constant remodeling by the processes of mitochondrial fusion and fission. These processes are known to be essential for cell survival, as knocking out various protein components of the machinery controlling mitochondrial dynamics usually leads to a lethal phenotype [50, 51]. In fact, mitochondrial dynamics participate in processes such as mitochondrial biogenesis, mtDNA maintenance, cell metabolism, cell proliferation, cell survival, and ultimately cell death [52]. Although the regulation of mitochondrial dynamics is beyond the scope of this review, several recent reviews provide a thorough analysis of this topic [53, 54•].

Mitochondrial fusion is a two-stage process, involving outer membrane fusion (depending on the large GTPases Mfn1 and Mfn2) and inner membrane fusion, which depend on the dynamin-related protein Opa1. Mfn2 is abundantly expressed in the heart and is involved critically in cardiomyocyte apoptosis [55]. Overexpression of Mfn2 promotes mitochondrial fusion and activates the intrinsic apoptotic pathway, as seen in ischemia/reperfusion models [56]. Conditional knock-out of Mfn2 on adult cardiomyocytes seems to foster mitochondrial tolerance to Ca^{2+}-induced MPTP opening and improves post- reperfusion recovery in an in vivo model [57]. Paradoxically, a dominant-negative form of Mfn2 increases ceramide-induced apoptosis in cardiomyocytes [58], which agrees with previous reports describing an anti-apoptotic role for proteins involved in mitochondrial fusion [59]. These conflicting results may be explained by the role of Mfn2 in multiple signaling pathways beyond mitochondrial shaping. In fact, a particularly intriguing role of Mfn2 involves establishing points of contact between mitochondria and ER. Recently, our group reported that during early stages of ER stress, mitochondria underwent perinuclear fusion, that was associated with increases in ATP levels, oxygen consumption, reductive power and mitochondrial Ca^{2+} uptake [60]. Loss of Mfn2 leads to decreased mitochondria-ER contacts, which may hamper the response to ER stress such as seen in cardiac hypertrophy [61]. Changes in the mitochondria-ER coupling appear also to be involved in pulmonary hypertension, a disease characterized by excessive proliferation of pulmonary artery vascular cells. Disruption of mitochondria-ER coupling by knocking out the ER-shaping protein Nogo B lead to resistance to hypoxia-induced pulmonary artery hypertension [62•]. Mounting evidence suggests a critical role of mitochondria-ER coupling in cell homeostasis [63]; however, the full implications of is interaction remain largely unknown.

Opa1 is the primary protein responsible for inner mitochondrial membrane fusion and cristae structure. During heart failure, Opa1 levels markedly decrease promoting a phenotype characterized by small mitochondria with few cristae; although the mechanisms leading to the decrease in Opa1 levels are unknown, no significant changes were seen in mRNA content, suggesting a post-translational mechanism [64•]. Interestingly, this phenotype is restricted to pathological hypertrophy/heart failure; in physiological hypertrophy, mitochondrial biogenesis is enhanced and the aforementioned changes are not seen [65].

Recently, data with haploinsufficient $Opa1^{+/-}$ mice have shown altered morphology of the mitochondrial network and altered MTMP function. Surprisingly, mitochondria in the heterozygous mice were larger and clustering of fused mitochondria was observed when compared with wild-type controls. $Opa1^{+/-}$ mice, after 6 weeks of transverse aortic constriction (TAC), had two-fold greater hypertrophic growth and a significantly reduced ejection fraction when compared with wild type mice [66]. This new evidence further reinforces the observations already described for Mfn2 that enhanced fusion of mitochondria may be deleterious in the onset of pressure overload.

Mitochondrial fission depends on the large dynamin-related GTPase Drp1. This cytosolic protein migrates to mitochondria and polymerizes forming spiral structures that

constrict the organelle leading to its fission [4]. Other outer mitochondrial membrane proteins, such as mitochondrial fission factor (Mff) or mitochondria fission 1 protein (Fis1), were also required for mitochondrial fission in mammals serving as scaffolds for assembly of the fission machinery [67]. Mutations in Drp1 results in a phenotype characterized by elongated mitochondria and impaired ATP synthesis leading to dilated cardiomyopathy in mice [68]. However, hypertrophic cardiomyocytes usually present small mitochondria, with decreased levels of Mfn2 and increased Drp1 and Fis1 expression [69]. In fact, mitochondrial fission may serve as an elegant link between ROS signaling and Ca^{2+}: increased Ca^{2+} promotes Drp1-dependent mitochondrial fission, increasing ROS production, as is seen in heart failure. Furthermore, the pro-hypertrophic Ca^{2+}-dependent protein CaN induces the fragmentation of mitochondria by promoting Drp1 dephosphorylation and its translocation towards mitochondria [70]. Concordant with these observations, the expression of a dominant-negative form of Drp1 (DrpK38A) avoids ischemia-induced fission and protects cardiomyocytes from cell death decreasing MPTP opening [71•]. Similar results had been described using a chemical inhibitor of Drp1 (mdivi) in an ischemia-reperfusion [72] and in a TAC model [73]. In both systems, mdivi protects from cell death and ameliorates TAC-induced hypertrophy. These results underscore both the relevance of mitochondrial dynamics in cardiomyocyte survival as well as our limited understanding of the regulatory processes beneath. Figure 1c depicts the principal changes in mitochondrial dynamics proteins associated with cardiac remodeling.

A recent development, which certainly will provide interesting answers, is the discovery of microRNA regulation of mitochondrial dynamics. In the normal heart, miR-499 is highly expressed, inhibiting Drp1 activation and mitochondrial fission. Cardiac specific overexpression of miR-499 decreases ischemia-reperfusion myocardial injury and inhibits pathologic remodeling decreasing collagen deposition [74]. Conversely, cardiomyocyte overexpression of miR-27b induces cardiac hypertrophy and ultimately heart failure, likely due to its ability to decrease PPAR γ signaling, a known regulator of mitochondrial function. Even more interestingly, the use of an antagomiR-27b attenuated TAC-induced hypertrophy [75]. Several lines of work are currently aimed at clarifying the intricate pathways of microRNA regulation, which may provide a valuable tool for future pharmacological interventions.

Conclusion

Mitochondrial function is critical for normal cardiomyocyte function. Derangements in mitochondrial dynamics, ROS signaling or mitochondrial Ca^{2+} handling have been associated with cardiac hypertrophy, heart failure and ischemia/reperfusion injury. The identification of suitable therapeutic targets to revert mitochondrial dysfunction associated with heart disease is an ongoing challenge that hopefully will help to alleviate the burden of the cardiovascular pandemic.

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