Published in final edited form as:

Curr Hypertens Rep. 2010 December ; 12(6): 418–425. doi:10.1007/s11906-010-0147-x.

Mitochondrial Fission and Autophagy in the Normal and Diseased Heart

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Abstract

Sustained hypertension promotes structural, functional and metabolic remodeling of cardiomyocyte mitochondria. As long-lived, postmitotic cells, cardiomyocytes turn over mitochondria continuously to compensate for changes in energy demands and to remove damaged organelles. This process involves fusion and fission of existing mitochondria to generate new organelles and separate old ones for degradation via autophagy. Autophagy is a lysosome-dependent proteolytic pathway capable of processing cellular components, including organelles and protein aggregates. Autophagy can be either nonselective or selective and contributes to remodeling of the myocardium under stress. Fission of mitochondria, loss of membrane potential, and ubiquitination are emerging as critical steps that direct selective autophagic degradation of mitochondria. This review discusses the molecular mechanisms controlling mitochondrial dynamics, including fission, fusion, transport, and degradation. Furthermore, it examines recent studies revealing the importance of these processes in normal and diseased heart.

Keywords

Mitochondrial dynamics; Mitochondrial fission; Mitochondrial fusion; Autophagy; Mitophagy; Metabolism; Hypertension; Heart failure

Introduction

Prolonged elevation of blood pressure leads to a variety of changes in myocardial structure, coronary vasculature, and conduction system of the heart. These changes result in cardiac hypertrophy, coronary artery disease, cardiac arrhythmias, myocardial infarction, and chronic heart failure. In short, hypertension remains the most common risk factor for cardiovascular morbidity and mortality [1]. Although the association between cardiovascular disease and changes in metabolism and mitochondrial function has long been recognized [2], new studies demonstrate that mechanisms controlling mitochondrial dynamics are important to maintain normal cardiac function and contribute to disease-related remodeling [3•].

Mitochondrial Function and Turnover

Because of a continuous high demand for energy, adult cardiomyocytes have extremely high mitochondrial density compared with other tissues. In addition to generating adenosine triphosphate (ATP) via oxidative phosphorylation, mitochondria carry out other critical and diverse functions [4]. They participate in the synthesis and the degradation of essential metabolites, heme and steroid synthesis, regulation of cell proliferation, maintenance of plasma membrane potential, Ca^{2+} signaling, and programmed cell death (apoptosis). Mitochondria are composed of an inner and outer membrane. The outer mitochondrial membrane (OMM) serves as a barrier to proteins larger than 5000 Daltons, so that the ionic environment of the intermembrane space reflects that of the cytosol. The inner mitochondrial membrane (IMM) is more impermeable and contains the multiprotein complexes of the electron transport chain (ETC). As electrons are transferred down the redox potential gradient from NADH and FADH_2 through ETC complexes I–IV to oxygen, energy is transferred as an electrochemical gradient across the IMM. Dissipation of the gradient drives the synthesis of ATP. Mitochondrial permeability transition (MPT) results in loss of mitochondrial membrane potential (MMP) and release of intermembrane components, including cytochrome *c* and/or apoptosis-inducing factor (AIF), which then activate apoptosis via a series of reactions.

Mitochondrial abundance results from a balance between synthesis and degradation. Mitochondrial biogenesis involves the growth and division of pre-existing mitochondria and is controlled primarily by the nuclear genome. The peroxisome proliferator-activated receptor gamma co-activator (*PGC-1 α*) is a master regulator of mitochondrial biogenesis and coordinately activates expression of metabolism-related genes as well as many genes known to protect against oxidative stress [5]. Overexpression of *PGC-1 α* in the myocardium results in a large increase in mitochondrial abundance and causes cardiomyopathy progressing to failure [6], demonstrating the need to maintain an appropriate balance in mitochondrial abundance. Mitochondrial degradation occurs primarily via macroautophagy (hereafter termed *autophagy*), a highly conserved lysosome-mediated process of protein and organelle recycling in which intracellular components are first surrounded by double membrane-bound autophagic vesicles [7]. These vesicles then fuse with lysosomes to deliver their contents for degradation via acid proteases.

Autophagy and Selective Mitophagy

Autophagy occurs in all eukaryotic cells and is induced by starvation, hypoxia, intracellular stress, hormones, or other developmental signals. Nonselective autophagy is an adaptive response to nutrient starvation; degradation of cytosolic components (including mitochondria) provides amino acids and lipid substrates for intermediary metabolism. Autophagy can also be selective for organelles and protein aggregates. Selective autophagic degradation of mitochondria is termed *mitophagy* and can be triggered by MPT pore opening and loss of mitochondrial membrane potential [7]. In cardiomyocytes (and in other

terminally differentiated, highly oxidative cells), there is a continuous basal-level, autophagic turnover of mitochondria.

Selective autophagy of protein aggregates and peroxisomes [8] involves ubiquitination of target proteins and recognition by adapter proteins, such as p62, that bind both ubiquitin and microtubule-associated protein 1 light chain 3 (LC3), a protein located in autophagic membranes. Although it is reasonable to postulate that mitochondria are targeted through a similar mechanism, this remains to be demonstrated. Because MPT pore opening can trigger mitophagy, many of the same processes that trigger apoptosis, such as Ca^{2+} overload and the generation of mitochondrial reactive oxygen species (ROS), also signal mitophagy. Thus, autophagy can protect cells from damaged mitochondria that might otherwise elicit an apoptotic cell death response.

Autophagy and Cardiac Function

Mice with a cardiac-specific disruption of Autophagy-specific gene 5 (*Atg5*), a gene essential for autophagy, develop premature age-related heart failure, indicating that autophagy is essential for normal cardiac function over the course of a life [9•]. Dysregulation of autophagy contributes to the pathogenesis of several diseases, including neurodegenerative disorders, skeletal myopathy, cancer, and microbial infection. Recent reports demonstrate that multiple forms of cardiovascular stress, including pressure overload, chronic ischemia, ischemia-reperfusion, and diphtheria toxin-induced injury, provoke an increase in autophagic activity in cardiomyocytes [10]. Transgenic mice haploinsufficient for the autophagy gene *Beclin 1* have reduced autophagic activity and improved cardiac function in the setting of heart failure induced by pressure overload, whereas mice carrying a cardiac-specific *aMHC-Beclin1* transgene, to increase autophagic capacity, are more sensitive to pressure overload [11]. This finding suggests that in the context of pressure overload, autophagy may be maladaptive. However, complete loss of autophagy, as in the mice with a cardiomyocyte-specific disruption of *Atg5*, results in increased sensitivity to pressure overload [12]. Thus, we postulate that the physiological impact of autophagy exists as a continuum, where either too much or too little autophagic activity can be detrimental [13]. Several lines of evidence suggest that basal levels of autophagy are adaptive, whereas stress-related increases in autophagy can be maladaptive. Mitophagy is likely to have this same dual nature, increasing myocyte survival in some contexts and contributing to type II autophagic programmed cell death in others.

Mitochondrial Dynamics

Electron micrographs give the erroneous impression that mitochondria are static organelles. Instead, mitochondria are actually highly dynamic, capable of traversing great distances in the cell along microtubules and undergoing constant fission and fusion events, forming real networks. The word *mitochondria* derives from the Greek words *mitos* (thread) and *khondrion* (small grain), high-lighting the prominence of this characteristic. The constant process of fission and fusion allows the exchange of proteins, lipids, and mitochondrial DNA, and facilitates the transmission of Ca^{2+} signals, mitochondrial membrane potential, and ATP across distances within the cell [14,15]. Regulated fission and fusion are essential for changes in mitochondrial abundance to meet the metabolic demands of a cell and to help segregate dysfunctional or damaged mitochondria prior to autophagic degradation via mitophagy (Fig. 1).

Mechanisms Controlling Fission and Fusion

Fission

Mitochondrial fission and fusion share many molecular features with scission of endocytic vesicles relying on several members of the dynamin superfamily of microtubule-based GTPase motors. During fission, the dynamin-related protein –1 (DRP1/DLP1/DNM1L) is recruited from the cytoplasm to mitochondria, docking with the fission protein 1 (FIS1) in the OMM [16]. DRP1 forms a large homo-multimeric ring encircling the mitochondrion, which then constricts in an energy-dependent manner until fission occurs. GTP hydrolysis is required for both constriction and disassembly of DRP1. A lysine-to-alanine mutation at amino acid 38 (K38A) in the N-terminal GTPase of DRP1 disrupts GTP hydrolysis and is frequently used experimentally as a dominant negative allele to block mitochondrial fission [17].

Diverse posttranslational modifications of DRP1 regulate mitochondrial translocation (reviewed by Santel and Frank [18]). Phosphorylation at Ser585 in the C-terminal GTPase effector domain (GED) by the cell-cycle-specific kinase Cdk1/cyclin B during mitosis promotes DRP1 translocation and fragmentation of mitochondria prior to the distribution of mitochondria into daughter cells. Phosphorylation by cyclic AMP-dependent protein kinase (PKA) at a Ser656, also in the GED, decreases GTPase activity and mitochondrial fission [19]. Phosphorylation of this PKA-dependent site is reversed by the Ca^{2+} /calmodulin-activated protein phosphatase calcineurin (CaN) [19]. Furthermore, phosphorylation by calmodulin-dependent protein kinase 1 (CaMK1) at Ser600 promotes translocation to mitochondria and increases the affinity of DRP1 for FIS1 [20]. Thus, two Ca^{2+} -dependent signaling cascades prominently involved in cardiac remodeling can promote mitochondrial fission.

Additional regulatory modifications include nitric oxide (NO)-dependent S-nitrosylation of DRP1, contributing to NO-induced mitochondrial fragmentation. Sumoylation by SUMO1 (SMT3 suppressor of mif two 3 homolog 1) protects DRP1 from degradation, facilitating mitochondrial fission. The protease SENP5 (SUMO/sentrin specific peptidase 5) cleaves SUMO1, maintaining mitochondrial morphology. Ubiquitination also plays a regulatory role. MARCH5 (membrane-associated ring finger [C3HC4] 5), an E3 ubiquitin ligase located in the OMM, interacts with and ubiquitinates DRP1 and FIS1 as well as the fusion-related proteins mitofusin 1 and 2 (MFN1/MFN2). RNA interference-mediated knockdown of MARCH5 results in mitochondrial elongation. The relevance of these posttranslational modifications to cardiac function and heart failure has not been explored.

Fusion

Fusion requires coordinated joining of both the OMM and IMM without release or mixing of constituents in the matrix and intermembrane space. OMM fusion is directed by MFN1 and MFN2, large GTPases located in the OMM. Mutations in *MFN2* cause Charcot-Marie-Tooth disease. Cytoplasmic coiled-coiled domains form hetero-oligomers and homo-oligomers to tether adjacent mitochondria to one another. Fusion requires GTP hydrolysis, as it has been observed that mutation of the GTPase domain of MFN2 results in an accumulation of tethered but unfused mitochondria [21]. MFN2 is also located in the endoplasmic reticulum (ER), where it helps to tether a close association between the ER and mitochondria, facilitating mitochondrial Ca^{2+} uptake from ER stores [22•].

IMM fusion is directed by another dynamin-family member, optic atrophy 1 protein (OPA1), found tethered to the IMM and in the intermembrane space [23]. Differential splicing of *Opa1* transcripts generates multiple variants [24]. In addition, proteolytic cleavage of OPA1 by a number of mitochondrial localized proteases, including presenilin-

associated rhomboid-like protein (PARL), disrupts OPA1 function and inhibits fusion. A normal mitochondrial membrane potential is required for fusion of IMM. Loss of membrane potential promotes cleavage and inactivation of OPA1, inhibiting the ability of the affected mitochondria to rejoin the mitochondrial network, effectively isolating it for autophagic degradation [25••]. Thus, maintenance of membrane potential and/or OPA1 function after mitochondrial fission can determine whether daughter mitochondria are retained or degraded. OPA1 is also important for maintaining the structure of cristae.

The Role of *PINK1* and *Parkin*

Recent evidence suggests that several genes associated with Parkinson's disease, such as *PINK1* and *PARK2*, are involved in mitophagy of damaged mitochondria [26••]. PTEN-induced putative kinase 1 (PINK1) is a serine/threonine kinase targeted to mitochondria. *PARK2* encodes Parkin, a cytoplasmic E3 ubiquitin-protein ligase. Upon loss of mitochondrial membrane potential, PINK1 is stabilized and recruits Parkin to mitochondria, promoting autophagic degradation of the organelle [27]. Surface ubiquitination of protein aggregates and peroxisomes targets them for selective autophagic degradation. By extension, it is postulated that Parkin provides a mitochondrial ubiquitin tag to direct mitophagy. Parkin can auto-ubiquitinate itself as well as the OMM proteins voltage-dependent anion channel 1 (VDAC) and MFN2 [28,29]. In addition, the Parkin protein contains a "ubiquitin-like" domain. Whether these ubiquitination events act primarily as targeting signals or whether they alter the activity of the modified proteins is not known. Ziviani and Whitworth [29] propose that mono-ubiquitination of MFN2 by Parkin could interfere with mitochondrial fusion, preventing a damaged mitochondrion from rejoining the mitochondrial network, whereas poly-ubiquitinated MFN2 could stimulate p62-directed autophagic degradation.

Mitochondrial Trafficking

In mammalian cells, mitochondria are transported along microtubules to areas of high energy demand or areas where Ca^{2+} buffering is required. Interaction of mitochondria with the molecular motors such as kinesin is mediated by a subclass of Rho GTPases, called "MIRO" for mitochondrial Rho (reviewed by Reis et al. [30]). The C-termini of MIRO1 and MIRO2 are anchored in the OMM. Facing the cytoplasm are two GTPase domains flanking a pair of Ca^{2+} -binding EF hands. Adaptor proteins GRIF-1 and OIP106 facilitate interaction between MIROs and kinesin motors. The EF domains of MIROs act as Ca^{2+} sensors, with Ca^{2+} binding disrupting the transport complex. High local concentrations of Ca^{2+} halt mitochondrial movement, thus retaining mitochondria at sites where ATP production and Ca^{2+} buffering are needed. Recently, both MFN2 and PINK1 have been identified as interacting with the MIRO complex.

Regulation of Mitochondrial Dynamics

Fission and fusion of the mitochondrial network is a constant process, but diverse inputs can cause subtle or catastrophic shifts in one direction or the other. Among these are cell cycle control, oxidative stress, changes in Ca^{2+} , metabolic state, and activation of pro-apoptotic pathways. These mechanisms do not act alone, as there is evidence of substantial cross-talk.

Cell Cycle Control

In mitotically active cells, complete fusion of the mitochondrial network during G1-S often precedes global mitochondrial fission in preparation for cell division and segregation of mitochondria to daughter cells [4]. This cycle of fission and fusion is no longer relevant for postmitotic adult cardiomyocytes but may help maintain mitochondrial integrity in other cell types in the heart. Studies in postmitotic neurons suggest that stress reactivation of some

components of cell cycle control may result in reactivation of mitotic mechanisms that promote fission [31]. Reactivation of the fetal gene program in adult cardiomyocytes is a hallmark of cardiac remodeling. It is speculated that stress activation of the fetal gene program and early response genes might similarly influence mitochondrial dynamics in heart failure.

Oxidative Stress

Oxidative and nitrosative stress induce fission. Mitochondria are the major site for the production of ROS in the heart and thus are susceptible to ROS-mediated damage to proteins, lipids, and DNA. In cultured neurons, inhibition of fission by overexpression of MFN or the dominant-negative K38A DRP1 mutant protects cells from ROS and NO-mediated insults, preventing mitochondrial fission and improving survival [31]. Studies in cultured myocytes show similar protection from ROS-mediated damage [32].

Ca²⁺ Regulation

Mitochondria play an important role in Ca²⁺ transport and homeostasis, so it may come as no surprise that Ca²⁺ features prominently in the regulation of mitochondrial dynamics. Figure 1 highlights many of the steps at which Ca²⁺ acts. These include the regulation of DRP1 recruitment by CaN and CaMK1 and Ca²⁺-dependent inhibition of MIRO-mediated mitochondrial translocation. Overexpression of the ER membrane protein p20 stimulates the release of Ca²⁺ from the ER, and subsequent DRP1 translocation [33]. Inhibition of mitochondrial Ca²⁺ uptake blunts fission, emphasizing the importance of inter-mitochondrial Ca²⁺ concentrations. Increased mitochondrial Ca²⁺ stimulates the activity of matrix dehydrogenases, fueling the electron transport chain and ATP production [34]. Ca²⁺ also activates mitochondrial NO synthesis, leading to an increase in localized NO production [34].

Metabolic Regulation

Mitochondrial dynamics and energy substrate metabolism are tightly linked (reviewed by Zorzano et al. [35]). Increased metabolic rates are associated with mitochondrial fusion and dense packing of cristae. Downregulation of the fusion proteins OPA1 or MFN leads to fragmented mitochondria with reduced membrane potential and oxygen consumption [35]. Importantly, overexpression of a fusion-deficient mutant MFN2 increases glucose oxidation and mitochondrial membrane potential, demonstrating that MFN2 can influence metabolism independent of fusion [35]. PGC-1 α , the master regulator of metabolism and mitochondrial biogenesis, also controls the expression of MFN2. Changes in fusion-related proteins have been observed in animal models and patients with type 2 diabetes [35]. MFN2 protein and mRNA are diminished in skeletal muscle and, contrary to what one might predict, levels of the OPA1 protease, PARL1, are also decreased [35]. The decrease in PARL may therefore be compensatory. High glucose levels stimulate ROS generation and mitochondrial fragmentation in H9c2 cardiomyoblasts, aortic smooth muscle cells, and neonatal rat cardiomyocytes [36]. Dominant-negative DRP1 blocks ROS generation and improves cell survival, suggesting that fission is necessary for ROS generation in response to high glucose [32]. Glucose deprivation of neonatal rat cardiomyocytes is likewise reported to stimulate ROS-dependent protein aggregation and increased autophagic activity [37]. Thus, both glucose overabundance and glucose deprivation of cardiomyocytes can induce autophagy, although not necessarily through the same mechanisms.

Apoptosis

Crosstalk between regulation of the mitochondrial network and apoptosis is extensive. Bax (BCL2-associated X protein), a pro-apoptotic member of the B-cell leukemia/lymphoma 2

(BCL2) family, colocalizes with MFN2 and DRP1 at fission sites (reviewed by Autret and Martin [38]). Knockdown of DRP1 or expression of dominant-negative DRP1 can inhibit cytochrome *c* release in response to apoptotic stimuli [38]. Bax-dependent release of the mitochondrial protein DDP/TIMM8 facilitates DRP1 translocation and mitochondrial fission prior to cell death [38]. However, mitochondrial fission itself does not invariably result in cytochrome *c* release or cell death, as loss of membrane potential and fission in response to the mitochondrial uncoupler carbonyl cyanide 4-(trifluoromethoxy) phenylhydrazone (FCCP) is reversible when the drug is removed [38].

BNIP3 (BCL2/adenovirus E1B interacting protein 3) and NIX (BCL2/adenovirus E1B interacting protein 3-like) are pro-apoptotic BH3-only proteins that induce cell death and autophagy. Mechanisms of their action in mitophagy are reviewed by Zhang and Ney [39]. BNIP3 translocates to mitochondria to disrupt membrane potential and promote autophagy, whereas NIX can promote mitophagy when localized to either ER or mitochondrial membranes. NIX is essential for mitophagy during erythroid development. In addition to their ability to disrupt mitochondrial membrane potential, NIX and BNIP3 may be directly involved in targeting mitochondria to autophagosomes through a protein-protein interaction with the autophagic protein GABARAP (γ -amino butyric acid receptor-associated protein).

Increased BNIP3 expression and mitochondrial depolarization contribute to ceramide-induced autophagic death of malignant glioma cells [40]. Ceramide treatment of neonatal rat cardiomyocytes induces DRP1 translocation and mitochondrial fission [41]. Doxorubicin, which induces cardio-myocyte death through ceramide generation, also promotes mitochondrial fragmentation [41]. Ceramide has been implicated in both ischemia-reperfusion and TNF α -induced cell death. Whether the effect of ceramide in these contexts is dependent on BNIP3 or mitophagy has not been determined.

Expression of BNIP3 is induced by cardiac hypoxia, but it appears to require additional posttranslational regulation for translocation to mitochondria. NIX expression is not induced by cardiac hypoxia but responds to activation of Gq/protein kinase C signaling. The hearts of mice with a double knockout of both NIX and BNIP3 have elevated mitochondrial content and progress to advanced dilated failure by 30 weeks of age [42•], demonstrating the need for these proteins to facilitate “mitochondrial pruning” during normal cardiac maintenance.

Mitochondrial Dynamics in the Normal and Failing Heart

Based on electron micrographs, mitochondria comprise about 35% of the volume of adult cardiomyocytes [3•]. Interfibrillar mitochondria are relatively uniform in size and shape, ranging from 0.5 to 1 μ m in width and 1 to 2 μ m in length. They are aligned in longitudinal rows between myofibrils, often spanning a single sarcomere from Z-band to Z-band. These mitochondria are located in close proximity to Ca²⁺ release sites. Subsarcolemmal and perinuclear mitochondria are less organized and more varied in shape and size; they differ in metabolic activity. Fission and fusion of the subsarcolemmal and perinuclear populations may be relatively unrestrained, but it is likely that the morphologic dynamics of interfibrillar mitochondria are more constrained. In contrast, the appearance and distribution of mitochondria in cultured neonatal cardiomyocytes is similar to that observed in other types of cultured cells undergoing continuous fission, fusion, and movement. These key differences in mitochondrial dynamics between neonatal and adult cardiomyocytes must be kept in mind when interpreting *in vitro* studies.

The relationship between mitochondrial dynamics and hypertension is almost unexplored. Some studies on the cardiac response to hypertension or its treatment have shown that bioenergetic compensation is integrated into cardiac adaptation. Failure to make appropriate

changes in mitochondrial properties may alter energy substrate metabolism or accelerate ROS production. Quantitative and qualitative changes in mitochondria are seen in a number of models of hypertension and cardiac hypertrophy [43]. Sustained activation of the renin-angiotensin system and the sympathetic nervous system in individuals with uncontrolled hypertension results in elevated circulating levels of angiotensin II and catecholamines. In experimental systems, angiotensin II can promote mitochondrial dysfunction, whereas sustained administration of isoproterenol for 7 days induces fission of cardiomyocyte mitochondria [44,45].

During heart failure, interfibrillar mitochondria may lose their connections to the cytoskeleton and sarcoplasmic reticulum [3•,46]. There is a reduction in size and density of interfibrillar mitochondria in rodent models of heart failure [47]. Chen et al. [48•] demonstrated a dramatic decrease in OPA1 protein levels in both failing human hearts and a rat model of heart failure compared with normal controls; changes in MFN1, MFN2, DRP1, and FIS1 protein levels were much less obvious. OPA1 mRNA levels did not change, suggesting a posttranslational mechanism. The number of mitochondria increased, but their size decreased, and the density of cristae decreased, consistent with OPA1-mediated activation of mitochondrial fission. Simulated ischemia in H9c2 cells causes a similar reduction in OPA1 protein levels.

When cultured adult and neonatal cardiomyocytes are treated with thapsigargin or potassium chloride to increase cytosolic Ca^{2+} , the mitochondria generate ROS and undergo rapid fission [49]. Dominant-negative DRP1 prevents both fission and ROS generation, suggesting that ROS is not immediately downstream of increased intracellular Ca^{2+} , but rather depends on a DRP1-mediated mechanism.

Ong et al. [50••] used a photoactivatable, mitochondria-targeted green fluorescent protein to track individual interfibrillar mitochondria in adult cardiomyocytes. They found numerous incidences of interconnected, elongated mitochondria spanning multiple sarcomeres. In simulated ischemia, mitochondrial membrane depolarization and repolarization occurred synchronously along the entire length of the elongated mitochondria. Simulated ischemia reperfusion of adult cardiomyocytes induced mitochondrial depolarization, fragmentation, and cell death. Mdivi-1, a pharmacologic inhibitor of DRP1, preserved membrane potential, prevented fission, and improved survival. Importantly, Mdivi-1 significantly reduced infarct size in an *in vivo* model of cardiac ischemia/reperfusion. This suggests that inhibiting mitochondrial fission is cardioprotective in the setting of ischemia/reperfusion and may provide a novel pharmacologic strategy.

Conclusions

Mutations in numerous genes involved in mitochondrial dynamics are associated with neurodegenerative disorders, including *PARK2* and *PINK1* (Parkinson's disease), *OPA1* (optic atrophy type 1), and *MFN2* (Charcot-Marie-Tooth disease). Interestingly, the protein products of most of these genes are even more abundant in cardiomyocytes than in neurons, suggesting that they play prominent roles in cardiac biology as well. Recent findings linking the functions of PINK1 and Parkin with mitophagy in neurons are particularly exciting, and we anticipate that the cardiovascular field will benefit tremendously from the wealth of mechanistic molecular insights emerging from the study of these diseases.

Many questions remain to be answered before it will be possible to pursue mitophagy as a viable therapeutic target for heart failure or other cardiovascular diseases. Perhaps foremost among these is determining when mitophagy is adaptive and when it is maladaptive. For instance, too much mitophagy may deplete the mitochondrial population so that it falls

below the level required for contractile activity or maintenance of cellular integrity, leading to a decline in cardiac function or even death of individual myocytes. Conversely, failure to remove damaged mitochondria could increase cellular damage from excessive ROS generated by defective mitochondria. Finding the most effective and beneficial nodal points for controlling mitochondrial dynamics represents an important challenge for future research.

Acknowledgments

This research was funded in part by the National Institutes of Health (to J.A.H. and B.A.R.), the American Heart Association (to M.L., J.A.H., and B.A.R.), the American Heart Association-Jon Holden DeHaan Foundation (to J.A.H.), FONDECYT 1080436 (to S.L.), and FONDAP 1501006 (to S.L.).

We would like to thank Dr. Randy McMillan and Dr. Thomas Gillette for critical reading of this manuscript.

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Fig. 1.

Schematic depicting upstream signaling pathways through which hypertension may promote remodeling of cardiac mitochondria via control of the fission/fusion cycle. After fission, daughter mitochondria may rejoin the mitochondrial network via fusion, may be transported to other regions of the cell, or may be degraded via selective mitophagy. Ca^{2+} -dependent steps are indicated in red. *α₁-AR* α-adrenergic receptor, *AT₁R* angiotensin receptor 1, *β-AR* β-adrenergic receptor, *CaMK1* calmodulin-dependent kinase 1, *CaN* calcineurin, *Cdk* cyclin-dependent kinase, *DRP1* dynamin-related protein 1, *ER* endoplasmic reticulum, *FIS1* fission protein 1, *MFN* mitofusin, *MIRO* mitochondrial Rho (GTPases); *OPA1* optic atrophy 1 protein, *PINK1* PTEN-induced putative kinase 1, *PKA* cyclic AMP-dependent protein kinase, *ROS* reactive oxygen species, *Ub* ubiquitin