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Review article

# A time to reap, a time to sow: Mitophagy and biogenesis in cardiac pathophysiology

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ABSTRACT

Balancing mitophagy and mitochondrial biogenesis is essential for maintaining a healthy population of mitochondria and cellular homeostasis. Coordinated interplay between these two forces that govern mitochondrial turnover plays an important role as an adaptive response against various cellular stresses that can compromise cell survival. Failure to maintain the critical balance between mitophagy and mitochondrial biogenesis or homeostatic turnover of mitochondria results in a population of dysfunctional mitochondria that contribute to various disease processes. In this review we outline the mechanics and relationships between mitophagy and mitochondrial biogenesis, and discuss the implications of a disrupted balance between these two forces, with an emphasis on cardiac physiology. This article is part of a Special Issue entitled 'Mitochondria'.



**Contents**



## 1. Introduction

Mitochondria function as cellular power plants essential for meeting the energetic demands of eukaryotic cells. Their role extends to regulating fuel utilization, calcium stores, intracellular signaling and cell death. Because of the broad range of cellular functions they are involved in, mitochondria inherently occupy an important position as mediators of cellular homeostasis. Consequently, this crucial position associates the dysfunction of mitochondria to the development of various human diseases. Notably, studies to dissect the etiology of Parkinson Disease (PD) were among the first to highlight the physiological consequence of having poor mitochondrial quality control. Genetic models strongly implicate mitochondrial dysfunction as a common feature in the development of this neurodegenerative disease that leads to the loss of dopaminergic neurons (reviewed in [1–5]). In support of this is the fact that aging increases the risk of developing PD, which correlates with higher incidence of mitochondrial DNA mutations in dopaminergic neurons [6]. Moreover, agents that induce mitochondrial toxicity have been shown to lead to PD-like symptoms in animal models [7].

The major chronic diseases we face today such as neurodegenerative diseases, cancer, aging, diabetes, and heart failure are accompanied by mitochondrial dysfunction, and in fact, many elements of these chronic

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diseases may be directly attributed to mitochondrial pathology [8]. Mitochondrial disorders may be inherited either through maternal transmission of an abnormal mitochondrial genome or through autosomal transmission of mutations in the nuclear-encoded mitochondrial genes. However, far more commonly, mitochondrial dysfunction is a consequence of derangements in the ordinarily robust systems that orchestrate and maintain the health and function of these vital organelles.

Mitochondrial quality control collectively describes the cellular systems used to maintain a population of optimally-functioning mitochondria. Mitochondria possess an internal protein quality control system to refold or eliminate misfolded proteins, comprising chaperones (Hps10, Hsp60 and others) and proteases (Lon and other AAA proteases). Import of nuclear-encoded proteins must be coordinated with the expression of mitochondrial subunits for proper assembly of oxidative phosphorylation (OXPHOS) complexes. Homeostatic control of this is mediated through the mitochondrial unfolded protein response (UPRmt), which is activated by an imbalance of nuclear vs. mitochondrial OXPHOS subunits [9]. Mitochondrial turnover is another integral aspect of quality control in which dysfunctional mitochondria are selectively eliminated through autophagy (mitophagy) and replaced through the expansion of preexisting mitochondria (biogenesis). Impaired mitochondrial quality control results in the accumulation of damaged mitochondria that may generate more reactive oxygen species (ROS), produce ATP less efficiently, have a lower threshold for cytochrome *c* release (apoptosis) or mitochondrial permeability transition pore (MPTP) opening (necrosis), or may release mitochondrial components (mtHSP60, oxidized mitochondrial DNA) into cytosol where its recognition by receptors for damage-associated molecular patterns (DAMP) activates inflammation. In this way, impaired mitochondrial quality control gives rise to a myriad of disease states. Mitochondrial quality control is critically dependent on autophagy; factors that impair autophagy, such as advanced age or the metabolic syndrome (MetS), will impact mitochondrial quality control and accelerate the development of chronic disease phenotypes. In this review, we focus on the mechanics of mitophagy and mitochondrial biogenesis, and discuss the interplay between these two forces. We then discuss the pathophysiological consequences with an emphasis on the heart.

## 2. Mechanics of mitophagy and mitochondrial biogenesis

### *2.1. Mechanics of mitophagy*

Autophagy is a lysosome-dependent cellular degradation system in eukaryotic cells that allows for the bulk recycling of unwanted cytoplasmic aggregate proteins or dysfunctional organelles [10]. Along with the ubiquitin proteasome system (UPS), autophagy is important for maintaining proteostasis in the heart [11]. Mitophagy is the selective targeting and removal of mitochondria through autophagy. While some authors refer to the general process as mitochondrial autophagy and use the term mitophagy to mean Parkin-dependent elimination of mitochondria, in this review we will use 'mitophagy' to indicate autophagic removal of mitochondria, and where appropriate, will specify Parkin-dependent mitophagy. Mitophagy plays a critical role in protecting the heart during ischemia/reperfusion injury [12–14]. Depolarization of mitochondria is a prerequisite for Parkin-dependent mitophagy, but mitophagy mediated by Bnip3 and NIX may be triggered through other pathways including reactive oxygen species (ROS) [15], which promote dimerization of Bnip3 (and potentially NIX) on the mitochondrial outer membrane [16]. Nutrient stress (fasting) activates AMPK and general autophagy, which is associated with production of ROS from mitochondrial complex I [17]; however, fasting-induced mitophagy is impaired in cyclophilin D-deficient mice [18], which have hyperpolarized mitochondria. Thus there are hints that mitophagy initiated by nutrient stress may be initiated by mitochondrial depolarization and Parkin translocation, but a role for ROS and Bnip3 is not excluded.

Parkin-dependent (macro)mitophagy has been commonly studied using chemical uncouplers of mitochondria such as carbonyl cyanide 4-(trifluoromethoxy) phenylhydrazone (FCCP) or carbonyl cyanide m-chlorophenyl hydrazone (CCCP). Cellular stresses such as ischemia also trigger mitochondrial depolarization [13], resulting in the stabilization of the serine/threonine kinase phosphatase and tensin homologue (PTEN)-induced kinase 1 (PINK1) on the outer mitochondrial membrane (OMM) and recruitment of the E3 ubiquitin ligase Parkin, key factors for mitophagy [19–22]. PINK1 and Parkin function as critical partners to mediate the clearance of dysfunctional mitochondria [23,24]. Another Parkin-dependent mechanism for degrading mitochondrial components is through mitochondria-derived vesicles (MDV), which transit to multivesicular bodies and eventually the lysosome, or to the peroxisome [25].

Mitochondrial dynamics (fusion and fission) also play a critical role in mitochondrial quality control, and the process is closely linked to mitophagy, where fission is favored and fusion is suppressed, enabling engulfment by autophagosomes. Fission of reticulate mitochondria into smaller fragments is essential for mitophagy to occur [26,27]. Key to this process is the dynamin-related protein 1 (Drp1), a GTPase in the dynamin super-family of proteins, which is recruited to the mitochondria and facilitates the process of mitochondrial fragmentation [28]. Fission 1 (Fis1) is another key player in mitochondrial dynamics that interacts with Drp1 to facilitate mitochondria fragmentation [29]. Mfn1 and 2, which promote OMM fusion, are ubiquitinated and targeted for elimination by the UPS. Optic atrophy protein 1 (OPA1), important for fusion of the inner mitochondrial membrane, is degraded during mitophagy by the inner membrane zinc metalloprotease OMA1, which has overlapping activity with matrix AAA proteases [30–32].

PINK1 is constitutively made and continuously degraded by the mitochondria-specific proteases presenilin-associated rhomboid-like protein (PARL) and mitochondrial processing peptidase (MPP). Loss of membrane potential across the inner mitochondrial membrane inactivates PARL and MPP through an uncharacterized mechanism and permits the accumulation of PINK1 on the OMM. The kinase domain of PINK1 faces the cytosol and phosphorylates OMM proteins facilitating the recruitment of the E3-ubiquitin ligase Parkin [33–35]. PINK1 has been reported to phosphorylate a number of targets including Parkin itself [36,37], mitofusin 2 (Mfn2) [15], and mitochondrial rho 1 (MIRO) [38], a component of the microtubule-associated motor complex that anchors kinesin to mitochondria. Mfn2, which functions in mitochondrial fusion events and links endoplasmic reticulum to mitochondria, functions as a Parkin receptor after phosphorylation by PINK1, thereby recruiting Parkin to the mitochondria, where it ubiquitinates a number of OMM targets. Voltage-dependent anion channel 1 (VDAC1) has been shown to be a Parkin target essential for mitophagy [19], although this finding has been contested [39]. Ubiquitination and proteasomal degradation of MIRO, Mfn2, and Mfn1 serve to immobilize the mitochondrion and prevent it from rejoining the mitochondrial network through fusion [15,38,40–42]. Ubiquitination of OMM proteins facilitates recruitment of autophagy adapter proteins such as neighbor of BRCA1 (NBR1) or sequestosome-1 (p62/SQSTM1). These bifunctional adaptor proteins have an ubiquitin binding domain (UBA) and microtubule-associated protein 1 light chain 3 (LC3) interacting region (LIR) to bring the developing autophagosomal membrane in proximity to the tagged mitochondrion in a zipper-like process [43,44]. SMAD-specific E3 ubiquitin ligase 1 (SMURF1) has also been linked to Parkin-dependent mitophagy [45]. Surprisingly, its ability to facilitate mitophagy has been found to be independent of its E3 ubiquitin ligase function. Another Parkin-interacting autophagy promoter, activating molecule in Beclin 1-regulated autophagy (Ambra1) dissociates from mitochondrial Bcl-2 to bind Beclin1 to initiate autophagy [46,47]. Ambra1 interacts with Parkin to promote mitophagy, but is not a substrate of Parkin [48].

Mitophagy that is independent of PINK1/Parkin/ubiquitin can be initiated through atypical members of the Bcl-2 homology domain 3 (BH3) family members such as BCL2/adenovirus E1B 19 kDa protein-

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