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Mitophagy and Mitochondrial Quality Control Mechanisms in the Heart

Roberta A. Gottlieb, M.D.^{*} and Amandine Thomas, Ph.D.

Cedars-Sinai Heart Institute, 127 S. San Vicente Blvd. AHSP9313, Los Angeles, CA 90048

Abstract

PURPOSE OF REVIEW—Mitochondrial homeostasis and quality control are essential to maintenance of cardiac function and a disruption of this pathway can lead to deleterious cardiac consequences.

RECENT FINDINGS—Mitochondrial quality control has been described as a major homeostatic mechanism in cell. Recent studies highlighted that an impairment of mitochondrial quality control in different cell or mouse models is linked to cardiac dysfunction. Moreover, some conditions as aging, genetic mutations or obesity have been associated with mitochondrial quality control alteration leading to an accumulation of damaged mitochondria responsible for increased production of reactive oxygen species, metabolic inflexibility, and inflammation, all of which can have sustained effects on cardiac cell function and even cell death.

SUMMARY—In this review, we describe the major mechanisms of mitochondrial quality control, factors that can impair mitochondrial quality control, and the consequences of disrupted mitochondrial quality control.

Keywords

mitophagy; mitochondrial quality control; mitochondrial biogenesis; mitochondrial homeostasis; metabolic syndrome; heart disease

INTRODUCTION

Despite advances over the last 30 years, heart disease remains the leading cause of death in the world, according to the World Health Organization. Moreover, studies showed that the prevalence as well as the consequences of cardiovascular diseases can be different according to the sex, the age or other risk factors including obesity [1, 2] [3]. Understanding the molecular mechanisms involved in cardiovascular disease is thus still very important. Among these mechanisms, pathways involving mitochondria play a major role in heart physiology. Indeed, mitochondria constitute 30% of the cardiomyocyte volume and

^{*}Corresponding author.

Conflict of Interest

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cardiomyocyte function is closely associated with mitochondrial capacity, and mitochondrial dysfunction has been linked to cardiovascular diseases [4].

To preserve basal mitochondrial homeostasis and protect the heart under stress conditions, different mechanisms are involved in mitochondrial quality control, including mitophagy, mitochondria-derived vesicles, mitoproteases, and the mitochondrial unfolded protein response (UPR^{mt}), that we will describe in this review and conceptually summarized in Figure 1. Moreover, we highlight how the different conditions described before can contribute to cardiac injuries through a change in mitochondrial quality control. Loss of mitochondrial quality control can result in the accumulation of damaged mitochondria which can lead to heart dysfunction.

MITOCHONDRIAL QUALITY CONTROL

a-Mitophagy

Under normal conditions, Pink1 is imported into the mitochondria where it undergoes rapid cleavage and degradation at the inner membrane. When the mitochondria present a decrease of membrane potential, PINK1 accumulates on the outer membrane. PINK1 phosphorylates ubiquitin and other mitochondrial outer membrane proteins, facilitating Parkin translocation [5]. Parkin, an E3 ubiquitin ligase, ubiquitinates multiple outer membrane proteins. Ubiquitination of proteins allows recruitment of p62/SQSTM1. P62 is an adaptor interacting with ubiquitinated proteins and LC3, thereby recruiting a phagophore to engulf the ubiquitinated mitochondrion [6]. Recent studies showed the important role of other adaptors, Optineurin and NDP52, in PINK1-mediated mitophagy [7]. Finally, the autophagosome fuse with the lysosome to promote the degradation of damaged mitochondria including degradation of mitochondrial DNA (mtDNA) by DNase II, an acidic endonuclease. Mitophagy is also induced by Parkin-independent mechanisms involving proteins or lipids already present on the outer membrane of mitochondria. BNIP3 and BNIP3L/Nix, known for their role in apoptosis, interact directly with LC3 to initiate mitochondrial clearance [8, 9]. Finally, Fundc1 is a mitochondrial protein located on the outer membrane containing a binding domain for LC3 and participating in mitochondrial engulfment. These pathways are activated by different stimuli. Parkin-PINK1 pathway is induced by a decrease of membrane potential while Fundc1 has been reported to play a major role in the response to hypoxic stress [10]. Nevertheless, all of them may be involved in cardiac stress. Indeed, Parkin translocation to the mitochondria takes place during ischemia-reperfusion [11]. It has been suggested that infarction-induced mitophagy is a beneficial homeostatic response to protect the heart [12]. This is also supported by the lack of ischemic cardioprotection in Parkin-deficient mice [13]. Bnip3 is also activated during ischemia-reperfusion and triggers mitophagy [14].

b-Mitochondrial derived vesicles (MDVs)

Mitochondria can release small MDVs in order to eliminate specific mitochondrial proteins [15]. MDVs are generated through a selective incorporation of protein cargoes which can include only outer membrane protein or outer, inner and matrix proteins. These vesicles are independent of Drp1 and have a diameter between 70 to 150nm [15, 16]. MDVs are

produced in baseline conditions in cardiac H9C2 cells and in mouse heart tissue [17]. Stress increases the formation of these MDVs as observed after treatment with doxorubicin or antimycin A, in association with cardiac dysfunction [17, 18]. The formation of MDVs appears to be prior to mitophagy [15], suggesting a role for MDVs as a first defense before mitophagy, which is costlier for the cell. The PINK1/Parkin pathway was recently implicated in MDV formation [19]. MDVs are delivered to either late endosome or peroxisome. Lysosome-targeted MDVs contain oxidized protein and will be degraded [15, 20]. The MDVs directed to lysosome are dependent on the PINK1/Parkin pathway [18]. It has been suggested that protein import channel plays a major role in MDV formation, as import channels are where inner and outer membranes are closely approximated [19]. Other MDVs are delivered to the peroxisome but the reason why and the future of these vesicles are not known. Peroxisome-targeted MDVs contain mitochondrial E3 ubiquitin protein ligase 1 (MAPL) and involve endocytosis pathways [21, 22]. MDVs seem to be selective in term of cargo. Indeed, generation of ROS with X/XO stimulates the formation of MDVs which carry VDAC, but generation of ROS within the mitochondria using antimycin A produce MDVs without VDAC but with complex III [15]. This suggest that any mitochondrial protein can be a cargo.

c-Mitoproteases

Mitochondria possess multiple proteases essential for processing imported proteins. Among the intrinsic (resident in mitochondria) mitochondrial proteases (mitoproteases), there are 12 metalloproteases, 7 serine proteases, and 1 cysteine protease [23]. They are important for assisting in protein import, and additionally regulate the turnover of short-lived regulatory proteins, as well as participating in protein activation, mitochondrial biogenesis, and protein quality control. While this topic could easily fill an entire review, we will focus on the mitoproteases that are most important in mitochondrial protein import and quality control. The mitochondrial processing peptidase complex, comprising PMPCB (aka β -MPP) heterodimerizes with PMPCA, which binds the presequences of hundreds of proteins imported into the mitochondrial matrix, which are then cleaved by β -MPP. There are also proteases in the inner membrane facing into the intermembrane space that remove hydrophobic sorting signals from proteins delivered to the intermembrane space, notably IMMP1L and IMMP2L. With respect to protein quality control, ATP-dependent proteases (ATPases associated with diverse cellular activities, AAA) degrade mitochondrial proteins that have not been incorporated into complexes, are misfolded, or damaged by reactive oxygen species. These include mAAA protease, Lon protease homolog (LONP), and Clp protease proteolytic subunit (CLPP). Proteins in the intermembrane space are subject to degradation by iAAA protease and two ATP-independent proteases in the inner membrane (Atp23 and HTRA2/OMI). Mitoproteases also play an important role in mitochondrial biogenesis. LONP is responsible for turnover of TFAM, the central regulator of mtDNA stability, replication, and transcription. mAAA protease participates in assembly of mitochondrial ribosomes and synthesis of the mitochondrially encoded OXPHOS subunits. Mitochondrial morphology is also regulated by mitoproteases. The intermembrane dynamin-like protein OPA1 is regulated by cleavage by both YME1L and OMA1, which also degrade one another; short OPA1 forms promote mitochondrial fission whereas long OPA1 forms support mitochondrial fusion. Wai et al. demonstrated that cardiac-specific ablation of the

m-AAA protease YME1L alters mitochondrial morphology and metabolism and causes heart failure in mice [24] OPA1 is also important for cristae morphogenesis [25]. Mitoproteases also play an essential role in mitochondrial turnover via mitophagy: PINK1 is constitutively imported and inserted into the inner membrane where it is proteolytically degraded by presenilins-associated rhomboid-like protein (PARL). Failure to import or degrade PINK1 leads to its accumulation on the outer mitochondrial membrane and activation of Parkin-dependent mitophagy. Outer membrane and intermembrane space proteins can be degraded by the ubiquitin-proteasome system [26].

α -UPRmt

Mitochondria possess two major chaperone proteins that assist protein folding in the matrix: mtHSP70 and HSP60-HSP10 [27]. Associated with the chaperone system, proteases described above recognize and degrade misfolded protein under normal conditions. Under stress, accumulation of misfolded protein occurs in the mitochondria leading to a mitochondrial unfolded protein response. This pathway is well described in *C.elegans* [28, 29] and more recently described in mammals [30, 31]. In *C.elegans*, accumulated misfolded proteins in the mitochondrion are degraded by the protease CLPP-1, the peptides are exported from the mitochondria by a membrane transporter, HAF-1. These peptides can block further mitochondrial protein import [28, 29]. On the other hand, ATFS-1 normally degraded in the mitochondria by the Lon protease, under stress condition, is translocated to the nucleus [32]. Two other cytosolic proteins, UBL-5 and DVE-1, assist ATFS-1 to activate transcription of UPRmt target genes like HSP-60, HSP-6, HSP-10 and CLPP-1 [28, 29]. ATFS-1 is also able to induce the transcription of genes involved in mitochondrial import, ROS detoxification, as well as glycolysis [32]. During UPRmt, there is a decrease of global protein translation linked to a decrease of eIF2 phosphorylation via GCN-2, in a ROS-dependent mechanism [33]. In mammals, the UPRmt is not yet well defined. It has been described that unfolded protein accumulation induces activation of JNK2 which triggers c-Jun binding to AP-1 element leading to transcription of CHOP and C/EBP β [34]. The dimerization of CHOP and C/EBP β allows that the dimer binds to UPRmt promoter constituted by a CHOP binding site associated with mitochondrial unfolded protein response elements (MUREs) [35]. 11 genes contain these MUREs: chaperones (hsp60, hsp10, mtDnaJ), proteases (ClpP and YME1L1), import complex subunit Tim17A, and mitochondrial enzymes (Thioredoxin2, cytochrome *c* reductase, endonuclease G, Ndufb2) [36]. Corresponding to GCN-2 in *C.elegans*, EIF2AK2 or dsRNA-activated protein kinase (PKR), phosphorylates eIF2 α and decreases translation activity in mammals [37]. The aim is to produce more chaperones and proteases to decrease the mitochondrial stress, while suppressing synthesis and import of other proteins. The induction of this transcriptional activation remains unclear, but recent studies demonstrated a pathway homologous to that of *C.elegans*. Among those, ATF5 seems to play in mammals the role of ATFS-1 in worms [31]. Homologous proteins for DVE-1 and UBL5 have also been described as SATB2 and SATB5 [28]. Another UPRmt pathway is induced when misfolded proteins are in the IMS, and ROS production will activate AKT responsible for an activation of ER α [38]. Little information about the impact of UPRmt is described in the context of heart diseases. Acute ischemia/hypoxia-reperfusion induces UPRmt in *C. elegans* [39] or endothelial cells [40] and can be a protective response. However, loss of the mitochondrial aspartyl tRNA-

synthetase encoding gene DARS2 in mice results in dysregulation of mitochondrial translation and strong cardiomyopathy associated with an increase of UPRmt markers [41].

FACTORS AFFECTING MITOCHONDRIAL QUALITY CONTROL

a-Age

Cardiac senescence characterized by defects in contractility, calcium handling, cell metabolism and mitochondrial function [42]. Aging heart is generally associated with mitochondrial dysfunction [43] and decreased protein quality control [44]. Failure of protein maintenance is a major contributor to the age-associated accumulation of oxidized proteins, increase of protein carbonylation [45, 46], and increased mtDNA mutations [47]. Defects in proteostasis have been described in cells under normal aging [48]. Features of cardiac aging include decreased autophagy, increased protein oxidation and damage, accumulation of ubiquitinated proteins, aggregates and lipofuscin, an indigestible leftover of lysosomal degradation arising from iron-catalyzed oxidation/polymerization of protein and lipid residues [49–51]. Accumulation of mtDNA mutations induces an age-dependent cardiomyopathy [46, 52] with LV hypertrophy, cardiac dysfunction and fibrosis. Diminished mitophagy is also a major feature of aging [53]. Failure to clear senescent mitochondria is associated with cardiac aging [54]. Aging mice show a decline in beclin-1 and p62 in skeletal muscle [55]. PINK1 and Parkin are also associated with aging and lifespan. Deletion of Pink1 in flies shortens their lifespan and make them more sensitive to stress [56], in accordance with an accumulation of damaged mitochondria in aging myocytes associated with Parkin deficiency [57]. In the same way, longevity, in *C. elegans* and mice, is associated with UPRmt activation [58].

b-Obesity

Obesity is known to increase the risk of myocardial infarction and the following injuries in humans [3]. This susceptibility to ischemia-reperfusion injury has been reproduced in animal models [59, 60]. It remains unclear if mitochondrial dysfunction is the cause or the consequence of metabolic impairment, but it has clearly been associated with metabolic dysfunction in various metabolic tissues including pancreas, liver, skeletal muscle or adipose tissue [61, 62]. Indeed, development and aggravation of hepatic steatosis was found to be related to the decrease of mitochondrial β -oxidation [63]. Moreover, mitochondria appear to be involved in adipose tissue function through their role in different metabolic pathways like lipolysis and lipogenesis, and are recognized as one of the mechanisms involved in insulin resistance of this tissue [63]. Damaged and dysfunctional mitochondria seem to be a feature of obesity and metabolic disease, suggesting that mitochondrial quality control is impaired. For example, the loss of OMA1 in mice is associated with higher weight in these mice compared to wild-type and makes them more sensitive to gain weight on a high-fat diet (HFD) with increased adiposity [64]. In contrast, Parkin^{-/-} mice are resistant to a high-fat diet, with attenuated weight gain and less accumulation of lipids in liver and preservation of insulin sensitivity. Interestingly, wild-type mice subjected to HFD show increased Parkin in the liver, associated with upregulation of lipid transporters, which does not occur in Parkin^{-/-} mice [65]. Moreover, PINK1 and Parkin are up-regulated in vascular walls of obese mice and diabetic mice [66]. These results suggest that Parkin contributes to the diet-

induced obesity consequences, but it is still unclear how the mechanisms of mitochondrial quality control intervene in metabolic dysfunction. Indeed, decreased Parkin has been described in substantia nigra of HFD mice or db/db mice and appears to link PD and metabolic disease [67]. Among other mitochondrial quality control mechanisms, UPRmt has been described so far as a protective mechanism against lipid accumulation in liver [68] and a disruption of this UPRmt could contribute to insulin resistance [69].

c-Sex differences

Heart disease is more prevalent in men than in women even although it is the leading cause of death in women, and heart disease is underdiagnosed and undertreated in women [1, 2]. Mitochondrial dysfunction plays a major role in cardiovascular disease [4]; thus sex differences could impact mitochondrial function or mitochondrial quality control. Indeed, cardiac mitochondria of female rats showed a lower production of hydrogen peroxide than males [70]. Another study described that mitochondrial complexes III, IV and V in heart have a higher activity in female monkeys compared to males [71]. A proteomic study on heart tissues described differential gene regulation between male and female. Indeed, genes involved in fatty acid metabolism and in oxidative phosphorylation are differently expressed between sexes, but differences in gene expression can also be affected by age [72]. Moreover, female rats have a lower expression of apoptotic genes in hearts compared to males, which could protect the female heart [72]. Moreover, mitochondria of female hearts are less sensitive to calcium [73] and possess differences in structure and respiratory function compared to males [74]. One mechanism that may contribute to the differences in mitochondria between males and females is that estrogen regulates mitochondrial biogenesis, oxygen consumption, and energy production [75]. Less is known about how sex differences affect mitochondrial quality control, but some recent studies focused on this link. For example, *Drosophila melanogaster* females can adapt to hydrogen peroxide stress but not to superoxide stress, whereas it is the contrary for the males, suggesting a sex-specific response depending on the stress. In addition, this sex-specific adaptation to a stress is associated with a sex-specific expression of Lon protease isoform and proteolytic activity [76]. In mice subjected to hypoxia-ischemia, mitophagy induction is higher in females than in males and the lower clearance of damaged mitochondria in males may contribute to their greater vulnerability to neuronal death after hypoxia-ischemia [77]. Interestingly, the ER α -dependent UPRmt pathway is higher in females than in males [77, 78].

d-Parkin-dependent mitophagy

The machinery governing mitophagy was discussed above, but in this section we will consider how mutations, post-translational modifications, or changes in the level of expression of key elements in the mitophagy pathway will alter mitochondrial turnover. Parkin mutations are responsible for some cases of early-onset Parkinson disease (PD). Mitochondrial dysfunction arises from impaired mitochondrial turnover, which manifests first in the dopaminergic neurons of the substantia nigra. However, dopaminergic neurons are not the only cells to suffer adverse consequences from Parkin mutations. Parkin knockout mice show impaired mitochondrial turnover and increased susceptibility to myocardial ischemia/reperfusion injury [11, 57], and an epidemiological study reported that elderly patients with PD have a 2-fold higher risk of heart failure [79]. Thus mutations of

Parkin, or a decrease in its expression level, will result in impaired mitochondrial turnover. Moreover, p53 has been shown to bind cytosolic Parkin to prevent mitophagy in the setting of doxorubicin exposure [80]. Interestingly, metformin has been shown to normalize Parkin-dependent mitophagy associated with high-fat feeding and elevated p53 [81].

e-Pathway overload

Autophagic elimination of mitochondria requires intact lysosomal function, functional autophagy machinery, and appropriate mechanisms for tagging mitochondria (Parkin-dependent ubiquitination). Therefore, defects of other steps in the pathway will also impact mitochondrial turnover. Thus endoplasmic reticulum stress is associated with impaired mitophagy and mitochondrial dysfunction [82]. Aggregates arising from protein misfolding disorders have been suggested to affect mitochondrial function directly and indirectly. For instance, mutant huntingtin (mHtt) interferes with mitochondrial protein import (which could upregulate PINK1 activity at the mitochondrial outer membrane), but also affects mitochondrial transport (which could block mitophagy (reviewed in [83]). Enhancing autophagic clearance of aggregates results in improved mitochondrial function [84], suggesting that there may be competition for autophagic resources.

f-Balancing destruction with biogenesis

It is important to realize that cellular homeostasis requires replacement of mitochondria cleared via mitophagy. Indeed, the two pathways (mitophagy and biogenesis) are tightly linked. PGC-1 α is a transcriptional activator of mitochondrial biogenesis as well as TFEB, the key transcriptional controller of autophagy. Parkin regulates mitophagy but also degrades Paris, a transcriptional repressor of PGC-1 α . Cells definitely have a mechanism (perhaps multiple) for sensing mitochondrial output, although it is unclear whether that output is ATP, a mitochondrial-derived peptide such as humanin [85] or MOTS-C [86], or another signal. A useful analogy is bacterial quorum sensing, which is used to coordinate and synchronize biofilm formation or expression of virulence factors or antibiotic resistance genes, and which is governed by the local density of the bacterial population. Bacteria secrete specific signaling molecules which are detected by receptors. When the concentration of molecules exceeds a threshold level, a new program of gene expression is activated. In the context of mitochondria, we might imagine that they produce a signaling molecule that suppresses mitochondrial biogenesis. However, in the setting of mitochondrial dysfunction or depletion by mitophagy, levels of the repressive molecule are lowered, permitting mitochondrial biogenesis to proceed. Excessive mitochondrial proliferation in skeletal and cardiac myocytes is a common feature of OXPHOS disorders (mitochondrial myopathies) [87], but is also encountered in some instances of heart failure [88]. Despite the proliferation of mitochondria, OXPHOS function is significantly impaired, suggesting that the cell senses the energy deficit or absence of appropriate signaling molecules and responds by driving mitochondrial biogenesis. It should be noted that other instances of heart failure are associated with dysfunctional mitochondria and diminished PGC-1 α signaling, suggesting that the cell senses adequate mitochondrial content despite impaired function. From these examples one can conclude that cardiac homeostasis requires intact signaling of mitochondrial function/content and biogenesis machinery. When the ability to sense or correct for mitochondrial dysfunction is lost, cardiac function will necessarily suffer.

CONSEQUENCE OF DISRUPTED MITOCHONDRIAL QUALITY CONTROL

a-Reactive oxygen species (ROS) production

Mitochondria is one of the principal sources of ROS in cell [89]. While it has been demonstrated that ROS mediate induction of mitophagy, it is also important to consider whether impaired clearance of damaged mitochondria or poor quality control, the consequence in chronic ROS production, with its associated signaling [90, 91]. Mitochondrial ROS production is involved in ischemia/reperfusion injury [92]. Moreover, a chronic exposure to ROS in heart will induce apoptosis and fibrosis leading to heart dysfunction and remodeling [93].

b-Mitochondrial DNA mutations

Under a cardiac stress, like ischemia/reperfusion, mitochondrial DNA can be oxidized and mutated. In contrast to the nucleus, mitochondria possess limited DNA repair machinery [94]. Mitochondria with damaged genomes should be eliminated to avoid transmission of mutated mtDNA [95]. If mitochondrial quality control is disrupted, mtDNA mutations will be retained and distributed across the mitochondrial network, leading to broader mitochondrial dysfunction. As mtDNA mutations are well known to give rise to cardiomyopathies, it is not surprising that acquired mtDNA mutations will lead to cardiac dysfunction [96].

c-Metabolic inflexibility, inability to adapt mitochondrial function

Metabolic inflexibility corresponds to the inability to switch between different energy substrates and it is a major feature of metabolic disorders [97, 98]. Mitochondrial dysfunction contributes to metabolic inflexibility [99]. In heart, the capacity to switch between fuels is coupled with cardiac contractility [100]. Sustained increase of fatty acid oxidation is a common feature of heart failure, suggesting a link between the cardiac disease and metabolic inflexibility. Treatment focusing on improving carbohydrate utilization in HF patients seems promising [101, 102].

d-Inflammation

Mitochondria, as remnants of a prokaryotic ancestry, can be recognized by cells as pathogens. Cardiolipin, *N*-formylated peptides, oxidized mitochondrial DNA, and CpG islands, and mtHsp60 are all recognized as danger-associated molecular patterns (DAMPs). Cellular injury can result in the release of mitochondrial constituents, and a relationship between plasma mtDNA and inflammation has been demonstrated [103]. TLR9 recognizes mtDNA, and failure to properly degrade mtDNA by lysosomal endonucleases results in exacerbation of pressure overload and accelerated progression to dilated cardiomyopathy [95]. mtDNA is vulnerable to oxidative damage, and 8-oxoguanosine-modified mtDNA is a ligand for the NLRP3 inflammasome responsible for processing interleukin-1 β . As a major source of intracellular reactive oxygen species (ROS), dysfunctional ROS-producing mitochondria also ramp up inflammatory signaling through ROS effects on NF κ B [104], a transcriptional activator of IL-1 β and other inflammatory cytokines.

CONCLUSIONS

Mitochondrial number and function are regulated at multiple levels. Individual protein quality is governed by specific protein chaperones and proteases. At the outer membrane, ubiquitination and proteasomal degradation are important. Bulk degradation of mitochondria is utilized when mitochondrial number is in excess, when there is global mitochondria dysfunction (e.g., ROS production or depolarization), and when it is developmentally programmed (e.g., during differentiation). Homeostatic mechanisms are brought into play following mitophagy, to restore mitochondrial number and energetic capacity. Factors that affect autophagy, such as age and obesity, similarly impact mitophagy and the subsequent mitochondrial biogenesis. A central concept is that of eliminating damaged and dysfunctional mitochondria followed by their replacement with better ones. Failure to execute mitophagy may leave mitochondrial number unchanged but the population of mitochondria may be inefficient and producing excessive reactive oxygen species. This will lead to organ dysfunction and upregulation of inflammatory signals. Thus, mitochondrial quality control is essential for organ and systemic well-being.

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Compliance with Ethics Guidelines

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Figure 1.

The different pathways of mitochondrial quality control (mitophagy, MDVs, mitoproteases, proteasome, and UPRmt) can be modified by conditions such as aging, obesity, genetic mutations, pathway overload, and sex differences. Disruption of the overall process of quality control will result in dysfunctional mitochondria with multiple consequences.