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REVIEW

Mitophagy and heart failure

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Abstract Cardiac mitochondria are responsible for generating energy in the form of ATP through oxidative phosphorylation and are crucial for cardiac function. Mitochondrial dysfunction is a major contributor to loss of myocytes and development of heart failure. Myocytes have quality control mechanisms in place to ensure a network of functional mitochondria. Damaged mitochondria are degraded by a process called mitochondrial autophagy, or mitophagy, where the organelle is engulfed by an autophagosome and subsequently delivered to a lysosome for degradation. Evidence suggests that mitophagy is important for cellular homeostasis, and reduced mitophagy leads to inadequate removal of dysfunctional mitochondria. In this review, we discuss the regulation of mitophagy and the emerging evidence of the cardioprotective role of mitophagy. We also address the prospect of therapeutically targeting mitophagy to treat patients with cardiovascular disease.

Keywords Mitophagy · Heart failure · Autophagy · Mitochondria

Introduction

Cardiac mitochondria are responsible for generating energy in the form of ATP through oxidative phosphorylation (OxPhos) and are crucial for cardiac function. Therefore, it is not surprising that mitochondrial dysfunction is considered to be a major contributor to the development of heart failure. Dysfunctional mitochondria are less efficient at generating ATP, produce excessive amounts of reactive oxygen species (ROS), and are more likely to activate cell death [1]. Although mitochondria generate ROS as a by-product of oxidative phosphorylation, they are also highly susceptible to ROS-mediated damage. For example, mitochondrial DNA (mtDNA) is susceptible to ROS due to its proximity to the respiratory chain in the mitochondrial inner membrane and the lack of protective histone-like proteins. Studies have found that cardiac mtDNA accumulates mutations with age, which contributes to mitochondrial dysfunction and development of age-related cardiomyopathy [2, 3].

To ensure a network of functional mitochondria, myocytes have quality control mechanisms in place that act at both the protein and organelle levels. Damaged mitochondrial proteins are degraded by proteases in the mitochondria and the ubiquitin-proteasome system [4]. If the degradation of damaged proteins is insufficient to rescue the mitochondrion, then, the organelle is engulfed by an autophagosome and subsequently delivered to a lysosome for degradation. This selective removal of impaired mitochondria by autophagosomes is known as mitophagy. Both autophagy and mitophagy are critical for cellular homeostasis [5–8] and adapting to acute unfavorable conditions such as starvation or ischemia [9–11]. Unfortunately, both of these processes are reduced with age, which leads to inadequate removal of dysfunctional mitochondria [6, 12]. In this review, we discuss the regulation of mitophagy and the emerging evidence of its role in cardioprotection. We also address the prospect of targeting mitophagy therapeutically to treat patients with cardiovascular disease.

Autophagy in the myocardium

Macroautophagy, hereafter referred to as autophagy, is the process by which cells segregate and degrade cellular proteins and organelles. The process of autophagy involves a double-

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membraned autophagosome that engulfs cytoplasm and organelles and then fuses with a lysosome for degradation [13]. The activation of a complex composed of BECLIN 1, vacuolar protein sorting (VPS) 34, and VPS15 leads to nucleation of a double-membrane structure called the phagophore, or isolation membrane [14]. Two ubiquitin-conjugating systems—microtubule-associated protein 1 light chain 3 (LC3) [15] and ATG12-ATG5-ATG16 [16]—are involved in elongation of the membrane. LC3 is also responsible for tethering the autophagosome to the cargo [17, 18]. The autophagosome then encloses around the cargo and fuses with the lysosome, where the contents are degraded by lysosomal enzymes [13].

Under normal physiological conditions, basal autophagy maintains homeostasis by degrading long-lived proteins and abnormal organelles. Impaired or dysregulated autophagy in the heart is a major contributor to development and progression of heart failure. For instance, loss of VPS34 in myocytes disrupts the initiation of autophagy and leads to impaired protein turnover, a disorganized mitochondrial network and contractile dysfunction [19]. Similarly, cardiac ATG5-deficient mice are unable to elongate the phagophore to form mature autophagosomes. These mice accumulate dysfunctional mitochondria, have disorganized sarcomeres, and develop cardiac hypertrophy [5]. In addition, the lysosomal-associated membrane protein 2 (LAMP-2) is required for the fusion between autophagosomes and lysosomes, and LAMP-2 deficiency causes accumulation of autophagosomes in myocytes, which leads to a lethal cardiomyopathy [20, 21]. Cathepsin-L (CTSL) is a lysosomal protease that plays a key role in degradation of lysosomal content. CTSL deficiency leads to impaired autophagic flux and development of dilated cardiomyopathy [22]. Collectively, these studies demonstrate that a functional autophagy-lysosomal pathway is critical for cardiac homeostasis.

Myocytes increase autophagic activity during stress to adapt to changes in nutritional and energy demands. Enhancing autophagy helps maintain ATP levels to sustain contractile force of the myocytes. For instance, acute exercise induces autophagy in skeletal and cardiac muscles of fed mice, whereas mutant mice that are deficient in exercise-induced autophagy have reduced endurance during acute exercise [23]. Fasting also leads to a rapid increase in cardiac autophagy and inhibiting autophagy depresses cardiac function in fasting mice [11]. In addition, autophagy is enhanced after a myocardial infarction to preserve cellular ATP levels in myocytes. Inhibiting autophagy reduces ATP levels and exacerbates post-infarct remodeling, whereas enhancing autophagy mitigates remodeling and cardiac dysfunction [24, 25]. It functions to selectively clear cytotoxic protein aggregates and damaged organelles as well. Increased autophagy is also able to attenuate cardiac hypertrophy in a mouse model of desmin-related cardiomyopathy [26].

However, excessive autophagy can be detrimental due to excessive degradation of critical proteins and organelles. Autophagy is rapidly activated in the heart in response to cardiac pressure overload and remains elevated for weeks [27]. In this setting, enhanced autophagy is detrimental to the myocardium. Similarly, chronic and excessive activation of autophagy in myocardial ischemia/reperfusion is also detrimental to the heart [9].

Regulation of mitophagy

Although originally thought to be non-selective, it is now clear that autophagy can selectively target protein aggregates [28] as well as organelles such as peroxisomes [29], endoplasmic reticulum [30], and mitochondria [31]. Mitophagy is the selective sequestration and degradation of mitochondria by autophagosomes and is important in clearing mitochondria both under baseline conditions and in response to stress.

PINK1/Parkin pathway

One important pathway involved in regulating mitophagy is the PINK1/Parkin pathway (Fig. 1a). When mitochondria are healthy, the serine/threonine kinase PTEN-inducible kinase 1 (PINK1) is immediately imported into the mitochondrial matrix by the translocase of the outer membrane (TOM) complex [32] where it is cleaved by mitochondrial processing proteinase (MPP) and presenilin-associated rhomboid-like (PARL) [33]. However, upon loss of mitochondrial membrane potential, PINK1 ceases to be imported and instead accumulates on the outer mitochondrial membrane [33]. This leads to recruitment of the E3 ubiquitin ligase, Parkin, from the cytosol to the mitochondrial membrane [34]. Studies have demonstrated that Parkin translocation is dependent on PINK1 [35–37]. At least two PINK1-mediated events are required to initiate Parkin-mediated autophagy: (1) PINK1 must phosphorylate Mitofusin 2 (MFN2) which then becomes a receptor for Parkin at the mitochondria [38] and (2) PINK1 must phosphorylate ubiquitin at Ser65 [35, 36, 39]. To date, only a few mitochondrial Parkin substrates have been identified and characterized, and these include hexokinase 1 [40], VDAC1 [41], MFN1 and MFN2 [42], and MIRO [43]. The functional importance of these substrates in Parkin-mediated mitophagy is still unclear and controversial. Studies indicate that there is a redundancy between substrates and that the loss of one substrate has little or no effect on Parkin-mediated mitophagy. It is not surprising that this redundancy exists in cells because it ensures clearance of mitochondria even if one substrate is downregulated or mutated. Moreover, it is likely that there are many additional Parkin substrates on cardiac mitochondria and future studies should focus on identifying these substrates.

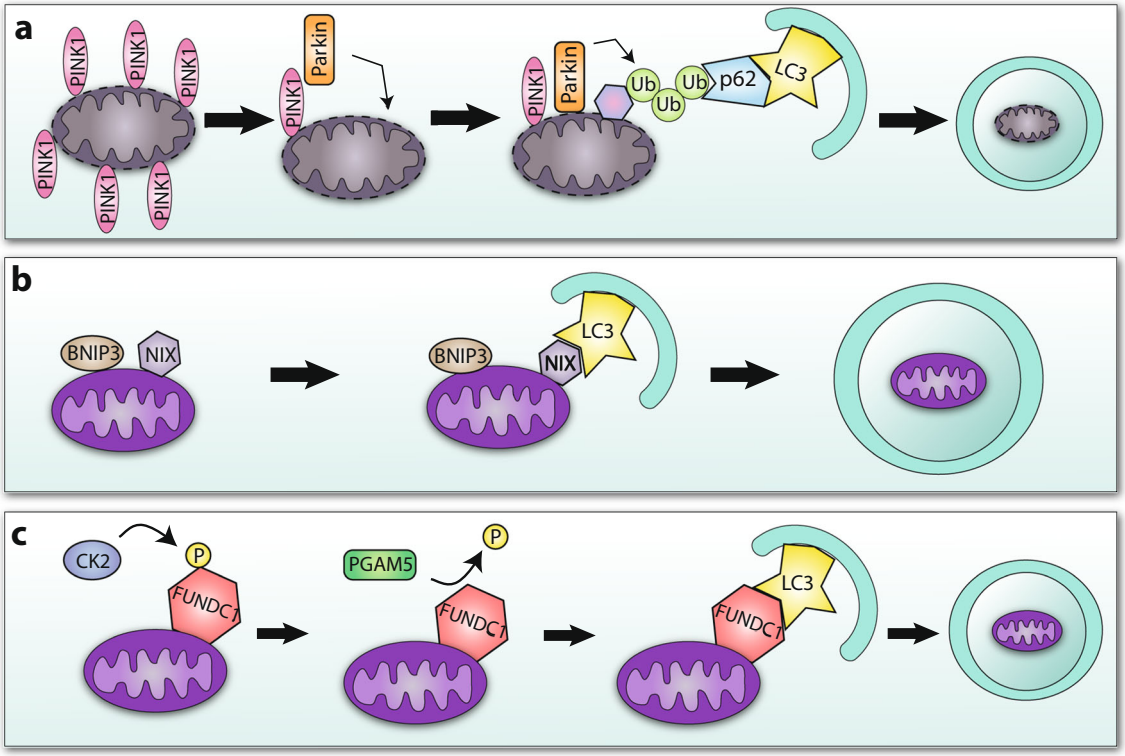

Fig. 1 Mechanisms of mitophagy. **a** Upon mitochondrial depolarization, PINK1 accumulates on the surface of the mitochondrion, recruiting Parkin to the outer mitochondrial membrane. Parkin polyubiquitinates mitochondrial membrane proteins, which allows them to be recognized by the adaptor protein p62. The autophagosome then engulfs the mitochondrion. **b** LC3 directly recognizes mitophagy receptor proteins BNIP3 and NIX resulting in mitochondrial clearance. **c** CK2 phosphorylates themitophagy receptor FUNDC1 to suppress its interaction with LC3. Hypoxia induces dephosphorylation of FUNDC1 by PGAM5, restoring its ability to interact with LC3 and trigger mitochondrial autophagy

Studies suggest that Parkin-mediated protein ubiquitination serves two purposes to facilitate mitophagy:

1. Ubiquitination of mitochondrial proteins via Lys63-linkage marks them for degradation by the autophagosome. Adaptor proteins such as p62 and NBR1 bind to LC3 on the autophagosome and to the ubiquitinated mitochondrial proteins, tethering the autophagosome to the mitochondrion [17, 44].
2. Ubiquitination of mitochondrial fusion proteins MFN1/2 via Lys48-linkage leads to their degradation by the UPS [42]. This causes a shift in the balance between mitochondrial fission and fusion towards fission. Fission increases the probability of the mitochondrial fragment being removed by mitophagy [45, 46].

Mitophagy receptor pathway

The mitophagy receptor pathway is another important but less well-characterized pathway that regulates mitochondrial clearance in cells. There are proteins present on the outer mitochondrial membrane that can function as autophagy receptors by directly binding LC3 on the autophagosomes. This pathway is independent of ubiquitination and adaptor proteins such as p62. BNIP3 [47], NIX [48], and FUNDC1 [49] are the only three mitophagy protein receptors that have been identified to date. Cardiolipin is a phospholipid that has also been found to interact with LC3. Cardiolipin is found exclusively in the inner mitochondrial membrane where it is essential for the function of many enzymes that are involved in mitochondrial energy metabolism [50]. Damage to mitochondria leads to redistribution of cardiolipin to the outer mitochondrial membrane which is associated with activation of apoptosis. However, a recent study demonstrated that the externalized cardiolipin can also interact with LC3 on the autophagosome and that this might prevent the activation of apoptosis [51].

Many studies have focused on the atypical BH3-only proteins NIX/BNIP3L and BNIP3 and their role in promoting cell death. It is now clear that these proteins also function to activate autophagy and mitophagy. NIX was first identified to act as a mitophagy receptor and is required for clearance of mitochondria in maturing erythrocytes [52]. Similar to the adaptor protein p62, BNIP3 and NIX contain LC3-interacting region (LIR) motifs and interact directly with LC3 on the autophagosome (Fig. 1b) [47, 48]. They can also directly

activate autophagy by disrupting the interaction between BCL-2 and BECLIN 1 [53]. BCL-2 maintains BECLIN 1 in an inactive state. Release of BCL-2 allows BECLIN 1 to form a complex with VPS34 and VPS15 to initiate formation of the phagophore [54]. Thus, BNIP3 and NIX can both increase the number of autophagosomes in the cells and facilitate selective removal of mitochondria. Unlike the PINK1/Parkin pathway, it is still unclear under what conditions these receptors induce mitophagy. A recent study by Glick et al. found that fasting of mice leads to significant upregulation of BNIP3 in the liver [55]. This raises the possibility that BNIP3 is responsible for selective mitophagy under starvation. Moreover, FUNDC1 is a more recently characterized mitophagy receptor (Fig. 1c). Under pro-survival conditions, Src kinase and CK2 phosphorylate FUNDC1, which suppresses its ability to interact with LC3 [56]. However, during hypoxia, FUNDC1 is dephosphorylated by the mitochondrial phosphatase PGAM5 allowing it to bind to LC3 to mediate mitochondrial clearance [49, 56].

The functional redundancy not only exists in the mitophagy receptor pathway, but also across pathways. Both NIX and BNIP3 overexpression induce translocation of Parkin to mitochondria [57, 58]. In addition, BNIP3-mediated mitophagy is reduced in Parkin-deficient myocytes [57], suggesting that the presence of Parkin is required for efficient clearance of mitochondria by BNIP3. Although the relationship between FUNDC1 and PINK1/Parkin or BNIP3 has not been investigated yet, it is possible that these pathways coordinate to ensure efficient mitochondrial quality control, especially during stress. For instance, a recent study reported that FUNDC1-mediated mitophagy is activated by ULK1 in response to hypoxia or by mitochondrial membrane depolarization by FCCP [59]. Interestingly, BNIP3 is well known to be upregulated by hypoxia and participates in hypoxia-mediated mitophagy [60], whereas Parkin-mediated mitophagy is activated by depolarized mitochondria [34]. Thus, activation of multiple pathways ensures efficient clearance of potentially harmful mitochondria during stress.

Mitochondrial dynamics and mitophagy

Mitochondria are dynamic organelles that undergo fission or fusion in response to changes in the cellular environment. MFN1/2 and OPA1 are involved in regulating mitochondrial fusion, whereas DRP1, FIS1 and MFF regulate fission [61]. Mitochondrial dynamics play an important role in mitochondrial quality control. For instance, mitochondria undergo fusion during starvation to maintain ATP production and protect them from mitophagy [62]. However, mitochondrial fusion is not always protective. Bhandari et al. found that re-fusion of damaged mitochondrial fragments that had escaped mitophagy can be harmful to myocytes [63].

In contrast, other studies have reported that fission is a prerequisite for mitophagy [46, 57, 64]. Mitochondrial fission allows for segregation of dysfunctional mitochondria. When photolabeled and tracked, mitochondria were found to divide asymmetrically, leaving one daughter mitochondrion with a lower membrane potential than the other. After asymmetrical fission, the mitochondrion with the higher membrane potential subsequently fuses with other healthy mitochondria, whereas the mitochondrion with the low membrane potential is less likely to re-fuse, and instead undergoes autophagic clearance [46]. Emerging evidence also indicates that proteins involved in mitophagy are able to stimulate mitochondrial fission. For example, overexpression of FUNDC1 induces mitochondrial fission, whereas knockdown leads to fused mitochondria [49]. Similarly, BNIP3 overexpression induces DRP1-mediated mitochondrial fission [57]. How these mitophagy receptors coordinate with DRP1 to induce fission is currently unknown.

Calcium signaling and autophagy

Calcium also regulates autophagic activity in cells. Adenosine monophosphate-activated protein kinase (AMPK) is a cellular energy sensor that is activated when energy levels are low. AMPK, in turn, activates autophagy to ensure survival during the nutrient scarce conditions [65]. Mitochondria and endoplasmic reticulum (ER) are closely associated in cells, and calcium released from the ER is efficiently taken up into the mitochondrial matrix by the mitochondrial calcium uniporter (MCU) [66–69]. Mitochondrial calcium uptake is important for effective oxidative phosphorylation and ATP synthesis [70]. Mitochondrial calcium uptake also regulates AMPK activity and activation of autophagy [68, 70]. For instance, when nutrients are abundant, the presence of growth factors activates cell surface receptors, which leads to generation of IP_3. IP_3 binds to IP_3R on the ER, which induces calcium efflux. Adjacent mitochondria take up the calcium and activate several key enzymes in the mitochondria, including pyruvate dehydrogenase, enzymes in the tricarboxylic acid cycle, and the F0F1 ATPase [71], resulting in increased ATP production. In contrast, when nutrients are scarce, less calcium is released and taken up by the mitochondria resulting in reduced energy production, activation of AMPK, and induction of autophagy (Fig. 2a). Several studies have demonstrated that abrogation of calcium release from ER or inhibition of calcium uptake into mitochondria results in reduced energy production and activation of autophagy under nutrient-rich conditions [68, 70]. Overall, these studies suggest that in the absence of ER-mitochondrial calcium transfer, cells turn on autophagy to sustain survival. However, how calcium levels regulate autophagy in cardiac myocytes still needs to be investigated.

Paradoxically, it has been reported that increases in cytosolic calcium also activate autophagy (Fig. 2b). Cytosolic

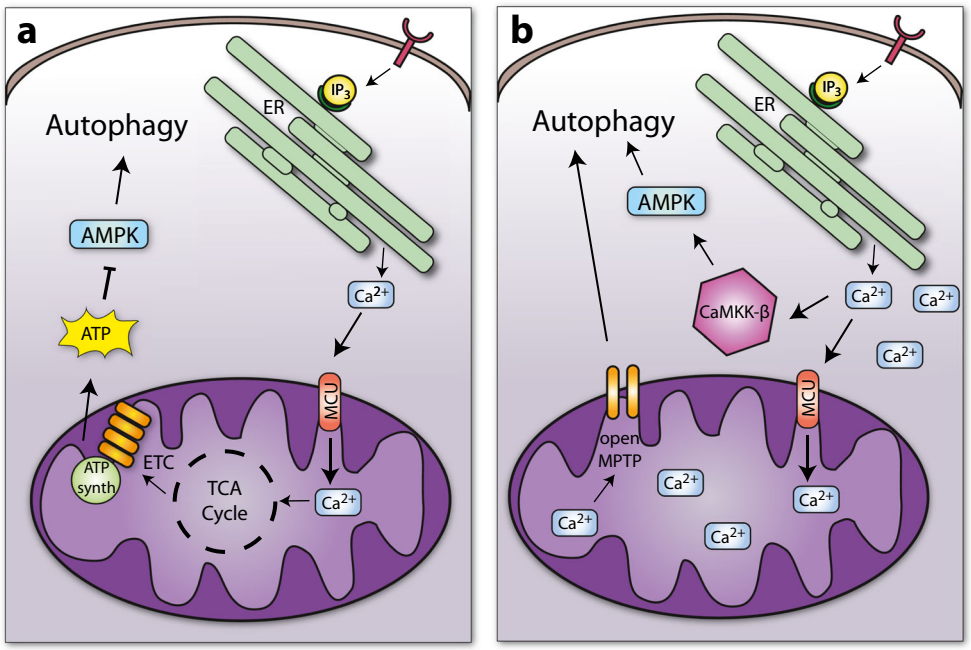

Fig. 2 Regulation of autophagy by intracellular calcium. **a** Mitochondrial uptake of calcium by the MCU results in increased ATP production, inhibition of AMPK, and suppression of autophagy. **b** Excessive levels of intracellular calcium leads to excessive mitochondrial calcium uptake, opening of the MPTP, and disruption of mitochondrial function. The reduced energy levels result in activation of AMPK and autophagy. Excess intracellular calcium also leads to direct activation of AMPK and autophagy via CaMKK-β

calcium activates the Ca^{2+}/calmodulin-dependent protein kinase kinase-β (CaMKK-β), which in turn activates AMPK [72, 73] and autophagy [74]. Additionally, excess uptake of mitochondrial calcium leads to opening of the mitochondrial permeability transition pore (MPTP) and collapse of the proton gradient [1]. Opening of the MPTP has also been linked to activation of autophagy and mitophagy [31, 75, 76]. Thus, different levels of cytosolic calcium have opposing effects on autophagy. At lower concentrations, calcium is taken up by mitochondria which promotes energy production and inhibits autophagy. In contrast, excess levels of calcium leads to direct activation of AMPK and autophagy via CaMKK-β and indirectly via excess mitochondrial calcium uptake.

Mitophagy in the heart

Mitophagy is a critical mitochondrial quality control mechanism in myocytes, and impaired mitophagy leads to accumulation of aberrant mitochondria and subsequent contractile dysfunction [6–8]. It is well established that loss-of-function mutations in the genes that encode *Pink1* or *Parkin* lead to the development of early onset Parkinson's disease [77]. More recent studies have demonstrated that a defect in PINK1/Parkin-mediated mitophagy also has negative consequences for the heart (Table 1). For instance, PINK1 deficiency in mice leads to cardiac mitochondrial dysfunction and enhanced oxidative stress [7]. These mice develop cardiac hypertrophy at 2 months of age. Although Parkin is the downstream effector of PINK1, $Parkin^{-/-}$ mice have a different cardiac phenotype. These mice have normal cardiac function when young [8], but accumulate abnormal mitochondria with age [6, 78]. The differences in cardiac phenotypes suggest that other E3 ubiquitin ligases can compensate for the lack of Parkin to some extent or that PINK1 has additional functions in myocytes. Moreover, hearts lacking the Parkin receptor MFN2 have reduced Parkin-mediated mitophagy as well as reduced contractility, increased hypertrophy, and heart failure by 30 weeks of age [79]. MFN2 has other critical functions in cells, including mitochondrial fusion [80] and tethering mitochondria to the ER [81]. This disruption of multiple processes likely accounts for the more severe cardiac phenotype of MFN2-null mice compared to the Parkin- and PINK1-deficient mice.

Many studies have demonstrated that overexpression of NIX or BNIP3 activates mitophagy in cells, including myocytes [57, 58]. However, the importance of BNIP3/NIX-mediated mitophagy in cardiac homeostasis was first demonstrated in mice deficient in NIX and NIX/BNIP3 [82]. Germline deletion of NIX in mice leads to development of cardiac hypertrophy and decreased cardiac function with age [82]. Mice deficient in both BNIP3 and NIX accumulate abnormal mitochondria and develop cardiac dysfunction at about twice the rate that NIX-deficient mice do [82]. Thus, BNIP3 and NIX have overlapping functions and play an important role in mitochondrial turnover in the heart. Taken together, these studies demonstrate that mitochondrial maintenance through the PINK1/Parkin and mitophagy receptor pathways is important for cardiac homeostasis and that the dysregulation of mitophagy leads to accumulation of abnormal mitochondria, loss of myocytes, and contractile dysfunction (Fig. 3).

Table 1 Mitophagy regulators and cardiac phenotypes

Model	Mitophagy	Phenotype	Ref
Parkin$^{-/-}$	Decreased	Increased sensitivity to MI and doxorubicin exposure, accumulation of dysfunctional mitochondria, and oxidative damage with age, reduced life span	[6, 8, 78]
Parkin TG	Increased	Increased life span, preserved cardiac function with aging	[6, 97]
PINK1$^{-/-}$	Not assessed	Mitochondrial dysfunction, cardiomyopathy, increased sensitivity to I/R	[7, 90]
BNIP3$^{-/-}$	Not assessed	Decreased apoptosis and cardiac remodeling in response to I/R	[93]
BNIP3 TG	Not assessed	Increased sensitivity to MI, increased apoptosis	[93]
NIX$^{-/-}$	Not assessed	Decreased cardiac remodeling and preserved cardiac function in response to pressure overload	[92]
NIX TG	Not assessed	Ventricular dilation, reduced cardiac function	[95]
BNIP3$^{-/-}$ Nix$^{-/-}$	Not assessed	Accumulation of dysfunctional mitochondria, development of cardiac hypertrophy, decreased cardiac function	[82]

Unfortunately, autophagy has been reported to decrease with age in tissues including the nervous system [83] and the heart [12, 84]. This leads to inadequate removal of dysfunctional mitochondria, which can generate up to tenfold more H_2O_2 than healthy organelles [85]. Oxidative damage to mitochondrial proteins, lipids, and DNA has been detected in the aged myocardium [86]. Parkin-mediated mitophagy is reduced with age [6] but the underlying mechanisms for this are unknown. Interestingly, Parkin contains several conserved cysteine residues that are vital for preserving its solubility [87]. Modification of these residues can lead to Parkin misfolding and aggregation [88]. A growing body of evidence indicates that misfolding is a major mechanism of Parkin inactivation in neurons [89]. Thus, it is possible that with age, the number of dysfunctional mitochondria exceeds the capacity of Parkin-mediated mitochondrial clearance, resulting in

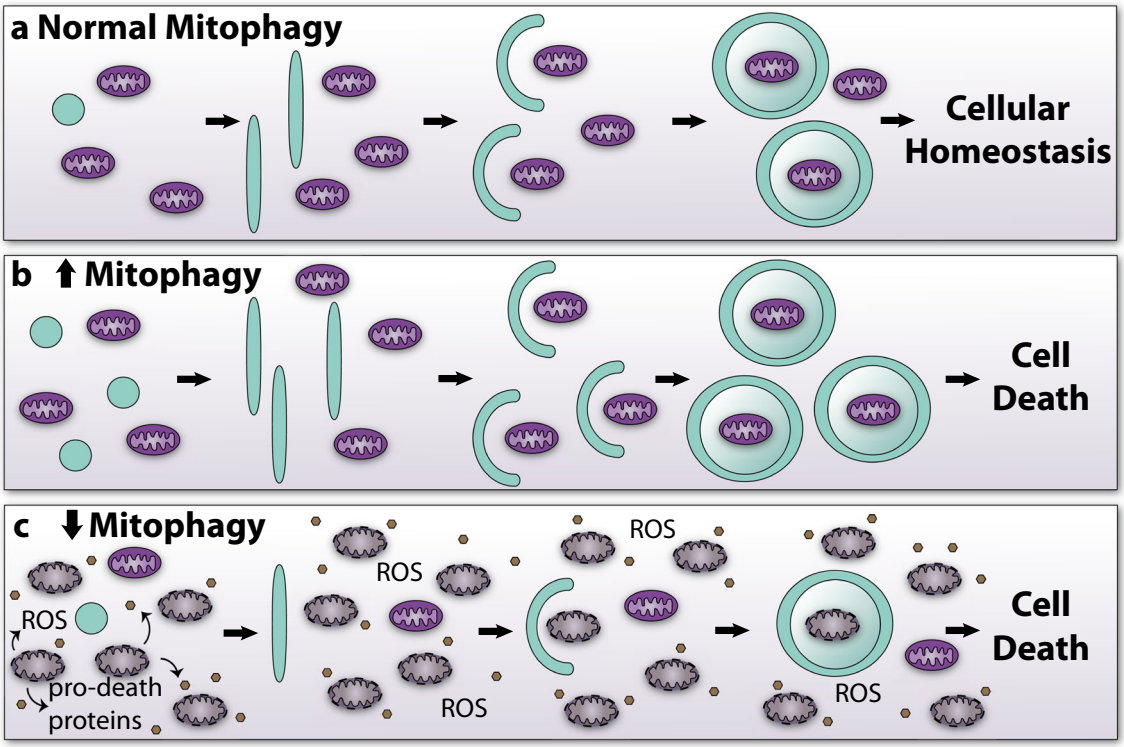

Fig. 3 Mitophagy and mitochondrial quality control. **a** Normal mitophagy begins with the initiation and elongation of a double-membraned autophagic vesicle. The vesicle then sequesters and engulfs mitochondria for degradation. Proper regulation of mitophagy leads to mitochondrial quality control and cellular homeostasis. **b** Increased mitophagy may greatly reduce the pool of functional mitochondria. With too few mitochondria, the cell loses its ability to produce sufficient energy and eventually dies. **c** A reduction in mitophagy causes accumulation of dysfunctional mitochondria. The dysfunctional mitochondria generate excessive ROS and release pro-death proteins, triggering rapid cell death

modification of Parkin and inhibition of mitophagy in the myocardium.

In addition, mitophagy plays an essential role in adapting to myocardial stress, and inadequate activation of mitophagy contributes to development of heart failure. Several studies have reported that mitophagy deficiency exacerbates cardiac injury in various experimental models of heart failure. For instance, Parkin deficiency leads to accumulation of dysfunctional mitochondria in myocytes, development of heart failure, and increased mortality after myocardial infarction in mice [8]. PINK1$^{-/-}$ mice are more susceptible to ex vivo I/R injury [90] and pressure overload-mediated heart failure [7]. Interestingly, PINK1 levels are reduced in human heart failure patients indicating inefficient mitophagy [7]. However, it is unknown if the reduced PINK1 levels are a cause or consequence of heart failure. Doxorubicin is an effective chemotherapeutic agent that is associated with cardiotoxicity. It is well established that doxorubicin causes mitochondrial damage in myocytes, which contributes to the loss of myocytes and development of heart failure [91]. A recent study demonstrated that doxorubicin exposure also impairs Parkin-mediated mitophagy [6]. It found that p53 binds and sequesters Parkin in the cytosol, which prevents it from translocating to mitochondria. This results in impaired clearance of dysfunctional mitochondria and subsequent development of cardiac dysfunction [6]. Thus, mitochondria-rich myocytes are particularly sensitive to doxorubicin compared to other cell types since doxorubicin induces mitochondrial damage and inhibits the ability to clear these mitochondria.

Although ablation of NIX and BNIP3 leads to impaired mitochondrial turnover, these proteins can be detrimental during stress. Cardiac-specific NIX-null mice have reduced cardiac fibrosis and preserved contractile function compared to wild type in pressure overload-induced heart failure [92]. BNIP3-deficient mice have reduced apoptosis and cardiac remodeling after myocardial infarction [93]. Similarly, a BNIP3 dominant negative protects against ex vivo I/R injury [94]. Additionally, cardiac-specific overexpression of NIX leads to activation of apoptosis in myocytes and development of heart failure [95]. The above data suggest that activation of BNIP3 and NIX in response to stress can be deleterious. It is possible that under baseline conditions, BNIP3 and NIX promote mitochondrial quality control through mitophagy. However, during certain conditions of cardiac injury, they become pro-death proteins instead. Under what conditions they switch from promoting mitophagy to promoting cell death still needs to be determined.

Conclusion and future directions

Under baseline conditions, reduced or dysfunctional autophagy is sufficient to cause cardiomyopathy [5]. Patients with diseases associated with dysfunctional mitophagy such as Danon's disease and Parkinson's disease often also develop heart failure [20, 96]. Because mitophagy levels decrease with age and heart failure is more prevalent in older populations, the possibility of therapeutically targeting mitophagy becomes more relevant as the global population continues to age. During cardiac stress and injury, mitophagy increases to help clear the damaged mitochondria and prevent oxidative damage and cell death [6, 8]. Therefore, it is possible that carefully controlled activation of mitophagy is the panacea for heart disease. Overexpression of Parkin in tissues has been shown to reduce age-associated cardiac dysfunction, increase life span, and preserve mitochondrial function in mice [6, 97]. However, it is important to consider that upregulation of mitophagy may not be beneficial in all circumstances. Mitophagy exists as a mitochondrial quality control mechanism and is important to maintain mitochondrial homeostasis. The beating cardiomyocytes depend on having a consistent pool of healthy mitochondria. With decreased clearance of damaged mitochondria, myocytes accumulate ROS and may die from mitochondrially triggered apoptosis. Increased mitophagy, however, may cause excessive mitochondrial clearance, leaving the myocytes with too few mitochondria to produce sufficient ATP. During acute cardiac injury, such as MI or I/R, a limited increase in mitophagy could be beneficial to clear damaged mitochondria. However, in chronic cardiac diseases, such as heart failure, sustained upregulation of mitophagy may be harmful and lead to excessive mitochondrial clearance. Thus, additional studies are needed to understand the regulation of mitophagy in myocytes and the consequences of short-term versus long-term upregulation of mitophagy on mitochondrial homeostasis, cell viability, and cardiac function.

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Disclosure None

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