Autophagy was initially considered to be a nonselective bulk degradation pathway, especially during stress such as starvation. However, given the critical role of mitochondria in maintaining cellular homeostasis, it is likely that degradation of mitochondria is a selective process during starvation.

Mitophagy is an essential housekeeping process that is required to maintain cardiac homeostasis. Studies suggest that mitophagy is important in eliminating impaired mitochondria both under baseline conditions and in response to stress (4, 9, 18, 32, 50, 82). Studies have linked impaired mitochondrial function and reduced autophagy to progression of heart failure and age-related cardiac pathologies (35, 61). Recent evidence also suggests a specific role for mediators of mitophagy in eliciting cardioprotective benefits (18, 32, 50, 82).

Activation of Autophagy

When mitochondria become damaged or functionally impaired, there is an increase in the number of autophagosomes in response to stress and aging. We also discuss the therapeutic potential of targeting mitophagy and directions for future investigation.

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the cell. This induction of autophagy occurs in discrete steps, and each step is regulated by a number of autophagy-related (Atg) proteins (Fig. 1) (44). A class III PI3K complex, composed of BECLIN 1(Atg6)/VPS34/VPS15, is responsible for nucleation of the isolation membrane (also known as the phagophore). The phagophore then elongates and two ubiquitin-like conjugation systems, ATG12-ATG5 and ATG8/light chain 3 (LC3), contribute to this step. Once this is complete, the mature LC3-II remains associated with the autophagosome membrane, where it interacts with specific adapter proteins or receptors that mark the mitochondria for degradation (52). The marked mitochondrion is then fully engulfed by the autophagosome. The final step involves autophagosome-lysosome fusion, during which acid hydrolase enzymes degrade the cellular content (44).

Targeting of Mitochondria to Autophagosomes

To ensure that healthy mitochondria are not sequestered and degraded by the autophagy-lysosomal pathway, dysfunctional mitochondria are selectively labeled or selected for degradation. To date, two different mechanisms of selective mitophagy have been described: phosphatase and tensin homolog induced putative kinase 1 (PINK1)/Parkin- and mitochondrial receptor-mediated mitophagy.

PINK1/Parkin-Mediated Mitophagy

The PINK1/Parkin pathway is involved in marking dysfunctional mitochondria for clearance by autophagy (Fig. 2A) (67). The serine/threonine kinase PINK1 is normally imported into healthy mitochondria by the translocase of the outer membrane (TOM) complex, where it is normally degraded by mitochondrial processing peptidase and presenilin-associated rhomboid-like protease (37). However, when a mitochondrion loses its membrane potential, import of PINK1 is abrogated. This leads to accumulation of PINK1 on the outer mitochondrial membrane and recruitment of the E3 ubiquitin ligase Parkin (37). The recruitment and activation of Parkin by PINK1 involve several steps. First, PINK1 phosphorylates mitofusin 2 (MFN2), which then acts as a mitochondrial receptor for Parkin (9). PINK1 must also phosphorylate ubiquitin to fully activate the E3 ubiquitin ligase activity of Parkin (40, 45). Activated Parkin is then responsible for ubiquitinating a number of proteins on the outer mitochondrial membrane. Parkin can mediate nonclassical K63-linked ubiquitination, which targets proteins for degradation by the autophagic-lysosomal pathway (21). The ubiquitin on these substrates serve as a signal for degradation. Adaptor proteins such as p62/SQSTM1 bind to the ubiquitinated proteins via its ubiquitin associated domain and to LC3 on the autophagosome (38). Parkin can also mediate the classical, proteasomal degradation-associated, K48-linked ubiquitination of mitochondrial proteins (52).

Mitochondrial proteins that are ubiquitinated by Parkin include MFN1/2, MIRO, Hexokinase I, and voltage-dependent anion channel (VDAC)1 (23, 70, 72, 88, 95). MFN1/2 and MIRO are shared PINK1 and Parkin substrates. They are phosphorylated by PINK1 before their ubiquitination by Parkin (88, 95). Interestingly, these substrates are degraded by the proteasome, which assists with the mitophagy process. Parkin-mediated degradation of the fusion proteins MFN1/2 maintains mitochondria in a fragmented stable, which facilitates mitophagy (88). Moreover, MIRO is a component of the complex that anchors kinesin to the mitochondria and Parkin-mediated degradation of MIRO leads to release of the damaged mitochondria from the tubulin network (95). The importance of MIRO in regulating mitophagy in myocytes still needs to be investigated. These studies suggest that UPS and autophagy pathways coordinate to clear dysfunctional mitochondria.

The importance of specific Parkin substrates in mitophagy is still unclear and controversial. For instance, silencing of VDAC1 with siRNA in HeLa cells reduces Parkin mitochondrial transloction and clearance (23). Similarly, Sun et al. (85) showed that all three VDAC proteins (1, 2, and 3) can recruit Parkin to damaged mitochondria and that their loss results in impaired mitophagy. However, a contrasting study found that VDAC1 is dispensable for mitophagy, and fibroblasts lacking both VDAC1 and VDAC3 eliminate mitochondria as efficiently as wild-type fibroblasts (66). This suggests that there is a redundancy between the different substrates to ensure degradation. Although only a few mitochondrial substrates have been identified to date, it is very likely that other still unidentified mitochondrial substrates of Parkin exist. Future efforts should focus on identifying novel Parkin substrates on mitochondria and elucidate their roles in mitophagy.
Cells have evolved mechanisms that negatively regulate Parkin-mediated mitophagy. For instance, the mitochondrial deubiquitinase USP30 opposes Parkin-mediated mitophagy by removing ubiquitin from Parkin substrates (5). Additionally, the anti-apoptotic B-cell lymphoma (BCL)-2 proteins, such as B-cell lymphoma-extra large (BCL-XL) and myeloid cell leukemia-1 (MCL-1), abrogate Parkin-mediated mitophagy by inhibiting Parkin translocation to depolarized mitochondria (28). MCL-1 and BCL-XL directly interact with Parkin in HeLa cells, and this interaction is increased after CCCP treatment (28). In contrast, Thomas et al. (90) found that PINK1/Parkin-mediated mitophagy is impaired in MCL-1-deficient hearts where deletion of MCL-1 in adult myocytes results in reduced PINK1 and accumulation of Parkin in the cytosol. Although these studies indicate that the anti-apoptotic BCL-2 proteins can regulate Parkin-mediated mitophagy, several questions need to be resolved. First, it is puzzling why anti-apoptotic proteins inhibit clearance of depolarized mitochondria since these organelles can activate apoptosis. The study by Hollville et al. (28) did not assess whether inhibiting Parkin-mediated clearance of damaged mitochondria has an effect on cell death. Also, it is unclear how loss of MCL-1 impairs the PINK1/Parkin pathway. Loss of MCL-1 leads to development of rapid heart failure, and it is unknown whether the impaired PINK1/Parkin pathway is a cause or consequence of the heart failure. Clearly, additional studies are needed to elucidate how the anti-apoptotic proteins regulate mitophagy in cells.

Mitochondrial Receptor-Mediated Mitophagy

BNIP3 and NIX. Another pathway involved in mitophagy occurs through the BCL-2-related proteins BNIP3 and BNIP3L/NIX. These atypical BH3-only proteins are well known activators of cell death. BNIP3 activates BAX/BAK in the outer mitochondrial membrane and causes opening of the mitochondrial permeability transition pore (49, 76, 94). NIX activates cell death via the mitochondrial apoptotic pathway (99) and induces necrotic cell death by perturbing endoplasmic reticulum/sarcoplasmic reticulum calcium stores (17). Interestingly, recent studies have identified an additional function for these two proteins where they act as autophagy receptors on mitochondria in cells. For instance, BNIP3 promotes mitophagy in various cells, including cardiomyocytes (26, 59, 74, 91). NIX is required for mitochondrial elimination in maturing reticulocytes (78, 81). Both BNIP3 and NIX localize to the outer mitochondrial membrane where they act as receptors for targeting autophagosomes to mitochondria (Fig. 2B) (27, 69). Using their conserved LC3-interacting region motifs, they can directly bind to LC3/γ-aminobutyric acid receptor-associated protein (GABARAP) on the autophagosome (27, 69), elimi-
nating the need for adaptor proteins. Because BNIP3/NIX and PINK1/Parkin play roles in mitophagy, this raises the question of whether they participate in the same pathway to clear mitochondria. However, the signals that activate the two pathways appear to be different. Whereas Parkin-mediated mitophagy requires loss of mitochondrial membrane potential (67), BNIP3 promotes mitophagy even when mitochondria retain their membrane potential (77). However, BNIP3 overexpression also induces translocation of Parkin to mitochondria in cardiac myocytes and Parkin-deficient myocytes exhibit reduced autophagy in response to BNIP3 overexpression (53). Additionally, NIX-deficient mouse embryonic fibroblasts have reduced Parkin translocation in response to CCCP treatment (15). Although these studies indicate potential coordination between BNIP3/NIX and the PINK1/Parkin pathways to clear mitochondria, the role and regulation of this potential crosstalk need to be investigated. In addition, in vivo mouse studies indicate that BNIP3/NIX is important for the normal turnover of mitochondria (18). Although it is clear that both BNIP3 and NIX are dual regulators of cell death and mitophagy, when and how they switch between these two opposing functions are unclear. It is also unknown whether other BH3-only proteins can function as autophagy receptors.

**FUNDC1.** FUNDC1 is an outer mitochondrial membrane protein that has been implicated in hypoxia-mediated mitophagy in mammalian cells (55). Similar to BNIP3 and NIX, FUNDC1 acts as a receptor and mediates mitophagy through its interaction with LC3 through its LIR motif (55). In contrast to BNIP3 and NIX, FUNDC1 does not have any pro-death activity. A recent study reported that the PGAM5 phosphatase dephosphorylates FUNDC1 during hypoxia or FCCP treatment, which promotes the interaction of FUNDC1 with LC3 and mitophagy (Fig. 2C) (8). Not surprisingly, new evidence show a link between the PGAM/FUNDC1 and the PINK1/Parkin pathways. Both PINK1 and Parkin are involved in familial Parkinson’s disease (14), and PGAM5-deficient mice develop a Parkinson’s disease phenotype (57). A recent study discovered that PGAM5 is required for stabilization of PINK1 on damaged mitochondria and that loss of PGAM5 abrogates PINK1-mediated mitophagy (57). In addition, both PGAM5 and BNIP3 play roles in hypoxia-mediated mitophagy (8, 91), raising the possibility that there is also cooperation between BNIP3 and PGAM5/FUNDC1 in regulating mitochondrial clearance in response to hypoxia.

**Cardiolipin.** Cardiolipin is present in inner mitochondrial membranes, where it is essential for optimal function of numerous enzymes involved in mitochondrial metabolism (33). Recently, it was reported that there is a significant redistribution of cardiolipin from the inner mitochondrial membrane to the outer mitochondrial surface during mitophagy (11). This study also reported that LC3 binds to cardiolipin on damaged mitochondria and that prevention of this interaction results in inhibition of mitochondrial delivery to autophagosomes (11). Thus it is possible that the redistribution of cardiolipin also acts as a signal for elimination of damaged mitochondria. These studies were conducted in neurons, and it will be necessary to determine whether cardiolipin regulates mitophagy in cardiac myocytes. It will also be interesting to investigate whether cardiolipin plays a role in activating other autophagy receptors or recruiting Parkin to mitochondria.

Overall, these studies demonstrate that multiple redundant pathways exist in cells to ensure clearance of dysfunctional mitochondria. These studies also indicate an intriguing link between different mediators of mitophagy, suggesting that these pathways may be more connected than previously thought. How these pathways coordinate mitophagy in vivo under baseline conditions and during stress still needs to be investigated.

**Mitochondrial Dynamics Regulate Mitophagy.** Mitochondrial dynamics have been implicated in regulating mitophagy. Studies have demonstrated that mitochondrial fission facilitates mitophagy (36, 39, 53, 92), whereas fusion protects against mitochondrial clearance (24, 75). Fission occurs in an asymmetric manner, which allows for segregation and degradation of only damaged mitochondrial components (92). The dynamin-like GTPase dynamin-related protein 1 (DRP1) plays a critical role in mediating mitochondrial fission and mitophagy. Deletion of DRP1 in cardiac myocytes results in mitochondrial elongation due to unopposed fusion, inhibition of mitophagy, and mitochondrial dysfunction, which lead to cardiac dysfunction and increased susceptibility to myocardial ischemia-reperfusion injury (36, 39). Mitochondrial fusion is regulated by Mitofusin 1 and 2 (MFN1 and -2) in the outer mitochondrial membrane and optic atrophy 1 in the inner mitochondrial membrane (12, 79). Fusion of mitochondria protects them from clearance by autophagosomes (24, 75). Interestingly, there is cross talk between the mitophagy and mitochondrial dynamics pathways. For instance, overexpression of BNIP3 leads to recruitment of DRP1 to mitochondria and induction of mitophagy (53). In addition, Parkin-mediated ubiquitination of MFN1/2 promotes their degradation by the proteasome (22, 72). This shift in the balance of fusion/fission proteins ensures that mitochondria are maintained in a fragmented state to allow mitophagy to proceed. Exactly how mitochondria coordinate with proteins involved in regulating their shape and clearance still needs further investigation.

**Damaged Mitochondria Signals to Induce Autophagy.** In addition to being marked for degradation, dysfunctional mitochondria must signal to the autophagy machinery to initiate the formation of additional autophagosomes. There are multiple ways this can be accomplished (Fig. 3). First, BH3-only proteins such as BAD, BNIP3, and NIX can directly activate autophagy by disrupting the BCL-2-BECLIN 1 interaction (3, 60). The anti-apoptotic BCL-2 proteins negatively regulate autophagy through their interaction with BECLIN 1 (60, 71), and the release of BECLIN 1 allows autophagy to be initiated (Fig. 3A). Similarly, Bax interacting factor-1 (Bif-1) is a positive regulator of Parkin-mediated mitophagy (86). This study found that Parkin translocation to damaged mitochondria is intact in the absence of Bif-1. Instead, Bif-1-deficiency results in accumulation of immature autophagosomes (86). In contrast, two other BH3-only proteins have been reported to have the opposite effect on autophagy. BIM and BMF localize to the cytoskeleton under baseline conditions where they inhibit autophagy (13, 58). BMF interacts with and stabilizes the BCL-2-BECLIN1 complex (13), whereas BIM sequesters BECLIN1 and prevents it...
from initiating autophagy (58). Thus this suggests that the regulation of autophagy by the BH3-only proteins might depend on their subcellular localization.

Additionally, when mitochondrial function is compromised, they produce less ATP, which leads to activation of AMPK and subsequent initiation of autophagy (Fig. 3B) (100). AMPK phosphorylates and activates the Unc-51-like kinase (ULK)1, which activates the BECLIN1/VPS34/VPS15 complex (42). ULK exists as two different isoforms: ULK1 and ULK2. Both can induce autophagy and have compensatory functions (10). However, recent studies indicate that ULK1 plays a specific role in regulating mitophagy (51, 96). In addition to activating the BECLIN1/VPS34/VPS15 complex, ULK1 translocates to mitochondria where it phosphorylates and activates the mitophagy receptor FUNDC1 (96). Interestingly, both ULK1- and NIX-deficient erythrocytes are unable to clear their mitochondria via autophagy (51, 81), suggesting that they act in the same pathway. It will be interesting to explore whether ULK1 is an upstream regulator of NIX and whether they coordinate to regulate mitophagy in other tissues including the heart.

ROS is a byproduct of oxidative phosphorylation, and myocytes have a great antioxidant capacity to neutralize the ROS. However, excess ROS from damaged mitochondria act as an important signal for mitophagy (Fig. 3C) (80, 83). Song et al. (83) recently reported that suppression of mitochondrial ROS in transgenic mice overexpressing a mitochondrial targeted catalase leads to impaired mitophagy in the myocardium. ROS can activate autophagy by inhibiting mammalian target of rapamycin (mTOR), a negative regulator of autophagy (1), or by activating BNIP3 (31, 48). Thus it is likely that a specific threshold for ROS levels exists in myocytes, and once that threshold has been reached, it signals activation of autophagy and mitophagy via inhibition of mTOR and activation of BNIP3.

Another mitophagy signal involves the mitochondrial permeability transition pore (mPTP) (Fig. 3D). Opening of this pore causes an influx of solutes and water into the mitochondrial matrix, which leads to disruption of the proton gradient and oxidative phosphorylation. It also causes depolarization and mitochondrial swelling that can activate autophagy.

**Fig. 3. Induction of autophagy by damaged mitochondria.** A: BH3-only proteins directly induce autophagy by disrupting the BCL-2/BECLIN1 complex to release BECLIN1. The BECLIN1/VPS34/VPS15 complex can then induce autophagy. B: damaged mitochondria produce less ATP production, which activates the energy sensor AMPK. AMPK then activates Unc-51-like kinase (ULK)1, which activates the BECLIN1/VPS34/VPS15 complex. C: damaged mitochondria produce reactive oxygen species (ROS) that inhibit mammalian target of rapamycin (mTOR). Inhibition of mTOR leads to activation of autophagy and mitophagy via inhibition of mTOR and activation of BNIP3. D: opening of the mitochondrial permeability transition pore (mPTP) results in influx of solutes and water into the mitochondrial matrix, which leads to disruption of the proton gradient and oxidative phosphorylation. It also causes depolarization and mitochondrial swelling that can activate autophagy.
and the interaction between Parkin and AMBRA1 is increased during prolonged mitochondrial depolarization (93). Although AMBRA1 is not required for translocation of Parkin to depolarized mitochondria, it is critical for subsequent mitochondrial clearance (84). Interestingly, AMBRA1 can also interact directly with LC3 through its LIR (LC3 interacting region) motif, and this interaction is critical for Parkin-dependent mitophagy (84). Surprisingly, specific targeting of AMRA1 to mitochondria leads to Parkin- and p62-independent mitophagy, suggesting that AMBRA1 can also act as a mitophagy receptor.

### Alternative Pathways of Mitophagy

Although traditional autophagy is dependent on Atg5 to form autophagosomes, recent studies have described an alternative Atg5-independent form of autophagy (68). This alternative form of autophagy is independent of Atg5 and Atg7 but, similar to autophagy, requires ULK1 and BECLIN 1 (Fig. 4A) (68). Unlike in traditional autophagy, the formation of autophagosomes occurs in a Rab9-dependent manner with vesicles derived from the trans-Golgi (68). This alternative autophagy pathway plays a role in clearing mitochondria during erythrocyte differentiation (29). This indicates that the Rab9-dependent alternative autophagy can also contribute to mitochondrial degradation. Additional studies are needed to determine the functional importance of this pathway in the myocardium, as well as its role in disease. It will also be necessary to decipher during what conditions traditional versus alternative autophagy are activated.

Microautophagy is another less known form of autophagy that occurs in mammalian cells. In this process, proteins and organelles are directly internalized into lysosomes through invaginations of the lysosomal membrane (Fig. 4B). Microautophagy has primarily been studied in yeast, but there is evidence that it also takes place in mammalian cells (65, 87). Nonselective microautophagy results in the degradation of randomly sequestered soluble intracellular material. This process has been observed in both yeast and mammalian cells (64). Selective microautophagy has only been described in yeast and involves the direct sequestration of organelles such as a mitochondria, nucleus, mitochondria, and peroxisomes into lysosomes (54). Currently, very little is known about the molecular mechanisms underlying microautophagy in mammalian cells. Its functional role in mammalian cells is not well understood, and it is unknown if alterations in this play a role in disease.

### Mitophagy and Cardioprotection

The half-life of mitochondria in the myocardium has been reported to range from days to weeks (43, 63). Thus mitochondrial degradation is critical for cardiac homeostasis, and interfering with this process leads to accumulation of dysfunctional mitochondria and cardiac dysfunction (4, 18, 32, 47, 50). Many studies have reported that autophagy is increased in the myocardium in response to stress, and this is initially a protective response activated by the cell (25, 62, 89). To date, few studies have focused on the specific role of mitophagy in the heart, but emerging evidence support a protective role for mitophagy in response to stress. Increased mitophagy was initially described in myocytes overexpressing BNIP3 and in hearts subjected to ex vivo I/R (26). Subsequent studies using knockout mouse
models have confirmed the importance of mitophagy in cardioprotection. For instance, PINK1-deficiency increased the susceptibility of the heart to I/R injury ex vivo (53). These mice also develop heart failure more rapidly in response to pressure overload than wild-type mice (4). Parkin-deficient mice accumulate dysfunctional mitochondria after a myocardial infarction, which leads to increased mortality (50). Parkin-deficient mice are also more susceptible to doxorubicin-mediated cardiotoxicity (32). In addition, Parkin plays a role in ischemic preconditioning, and Parkin null mice are resistant to preconditioning (34). This suggests that brief episodes of ischemia induce Parkin-mediated clearance of unstable mitochondria that are likely to cause damage during a prolonged ischemic episode. These studies clearly demonstrate the important cardioprotective role of mitophagy in the cardiovascular system, and enhancing mitophagy might represent a promising future therapeutic target.

In contrast, other studies have found that augmented autophagy can promote loss of myocytes (56, 62, 101). Although enhanced autophagy is protective during ischemia, it switches to a detrimental role during reperfusion (62). Increased autophagy is also detrimental in a model of pressure overload (101), confirming that chronic and excessive activation of autophagy can be dangerous to myocytes. Studies assessing the effect of chronic and excessive mitophagy in the myocardium are lacking, but excessive degradation of mitochondria in myocytes will be harmful. Hence, it will be important to determine the threshold of mitophagy in myocytes. It is likely that the levels and extent of both general autophagy and mitophagy determine whether it will be detrimental or beneficial to the cell. Excessive and/or prolonged induction of autophagy may be detrimental by causing overcleaving of organelles and critical proteins. Thus additional research is necessary to determine the dynamics that regulate this transition between autophagy-induced protection and cell death in the heart.

Recently, a study reported that Parkin-mediated mitophagy is protective in pancreatic β-cell function in diabetes (30). Diabetic cardiomyopathy is associated with mitochondrial dysfunction (6), and it is possible that impaired autophagy and mitophagy may contribute to the pathology. Interestingly, Xu et al. (97) reported that general autophagy, as well as PINK1 and Parkin protein levels, are significantly reduced in Type 1 diabetic hearts. Interestingly, this study noted that Rab9 is increased and that it colocalizes with mitochondria, suggesting that alternative mitophagy is increased to compensate for reduced traditional mitophagy. This implies that alternative mitophagy is independent of PINK1 and Parkin, a concept that needs to be further explored.

**Mitophagy in Aging**

There is a reduction in mitochondrial DNA (mtDNA) quality and mitochondrial function with age in most tissues (61). Unfortunately, autophagy is also reduced with age (35, 61). Parkin-mediated mitophagy is also reduced in senescent cells (32). Thus reduced autophagy and mitophagy in the aging myocardium could contribute to accumulation of dysfunctional mitochondria. In support of this, mice deficient in Parkin accumulate abnormal mitochondria in the myocardium at a much earlier age than wild-type and exhibit enhanced age-dependent accumulation of mtDNA deletion mutations and oxidative damage (32, 47). In contrast, overexpression of Parkin in myocytes increases mitochondrial turnover and delays age-related cardiac abnormalities (32). Additionally, increasing general autophagy in the heart systemically by overexpressing the critical autophagy protein Atg5 also delayed aging (73). These studies demonstrate the important cardioprotective role of autophagy and mitophagy in aging. However, although upregulation of mitophagy appears to be promising in combating the aging process, more research is necessary to fully understand its specific role in clearing mitochondria.

**Therapeutic Potential of Mitophagy**

Despite major advances in the treatment of cardiovascular diseases, there is still a need to find improved therapies. A future potential therapy includes targeting of autophagy, since many studies have reported that enhancing autophagy is cardioprotective. However, a major challenge is to find safe and efficient targets in the autophagy pathway. Many of the regulators of autophagy, such as mTOR and AMPK, also regulate other critical cellular processes, and modulating general autophagy via these pathways can produce unwanted off-target effects. There is also a concern that activating general autophagy will not result in the selective removal of damaged mitochondria.

Thus an alternate and novel approach would be to selectively target mitophagy to clear impaired mitochondria without increasing the general nonselective autophagy. This would help avoid chronic nonspecific cellular clearance and minimize off-target effects. Data from Parkin transgenic mice indicate that enhancing levels of Parkin in the heart have no adverse effects under normal conditions and the increased rate of mitochondrial turnover delays aging (32). However, it still needs to be investigated whether myocardial ischemia or pressure overload will be protective or result in excessive clearance in these mice. Although BNIP3 and NIX also promote mitophagy, they are more risky targets due to their pro-death activity. In fact, BNIP3 and NIX cardiac-specific transgenic mice have increased apoptosis, which leads to cardiac dysfunction (16, 99). Although current studies suggest that enhancing mitophagy is cardioprotective, a more in-depth characterization of the pathways involved is necessary to identify optimal therapeutic targets.

**Conclusion and Future Directions**

Our current knowledge of mitophagy in the heart is very limited, and a number of unresolved questions remain. For instance, studies suggest that enhanced mitophagy can protect against stress that acutely damages mitochondria. However, whether mitophagy will be cardioprotective in other chronic diseases such as diabetic cardiomyopathy, pressure overload, or late-onset anthracycline-mediated cardiotoxicity still needs to be investigated. Similarly, the threshold for mitophagy in myocytes is currently unknown, and it is unclear how much mitochondria can be cleared before the cells become energy deficient and activate cell death. Additionally, mitochondria that have been removed must also be replaced through biogenesis, and very little is known about how these two processes are connected. For optimal cardioprotection, future therapies should aim to increase mitophagy while simultaneously augmenting mitochondrial biogenesis to prevent mitochondrial

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depletion and cell death. In conclusion, although the majority of current studies support the concept that mitophagy is cardioprotective, additional studies are necessary before this pathway can be targeted therapeutically.

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