Mitochondria are evolutionarily preserved organelles found in almost all eukaryotic cells. The primary role of mitochondria in mammalian cells is adenosine triphosphate synthesis, which is achieved primarily through oxidative respiratory phosphorylation. Additionally, mitochondrial proteins also regulate innate immunity, apoptosis, necrosis, and autophagy. Adenosine triphosphate production through the respiratory chain is accompanied by production of reactive oxygen species (ROS) as a byproduct through leakage of electrons from the electron transport chain. Low levels of ROS are directly removed by antioxidants within mitochondria or actively stimulate counter-regulatory signaling/transcription pathways to maintain the proper redox balance. However, excessive accumulation of ROS during stress damages mitochondrial components, including mitochondrial DNA (mtDNA), protein, and lipids, which exacerbates ROS production and mitochondrial dysfunction in a feedforward manner. In response to ROS, mitochondria initiate and orchestrate various signaling mechanisms, thereby controlling the growth and death of various cell types. Damaged mtDNA that escapes from lysosomal degradation causes Toll-like receptor 9-mediated inflammation and myocarditis as a result of its immunomodulatory unmethylated CpG motifs. Mitochondria-derived excessive ROS eventually promote aging, carcinogenesis, neurodegenerative disorders, and cardiovascular diseases.

Because damaged mitochondria induce catastrophic consequences, the quality of mitochondria is essential and regulated by multiple mechanisms, including fission and fusion of mitochondria, degradation of mitochondrial proteins mediated by chaperones (Hsp10, Hsp60, and others), proteinases (Lon, AAA proteases), and proteasomes, and mitochondrial biogenesis. The constant production of ROS necessitates turnover and replacement of mitochondria every 10 to 25 days, even in the quiescent cell or organ. Increasing lines of evidence...
sugest that autophagy plays a major role in mediating mitochondrial quality control.10,11

Autophagy is a mechanism of cellular degradation through lysosomes. Autophagy is particularly important for cell survival during energy stress because amino acids and fatty acids recovered through degradation of cellular constituents by autophagy can be recycled to generate adenosine triphosphate. Autophagy is classified into 3 categories: macroautophagy, microautophagy, and chaperone-mediated autophagy.15-14

Macroautophagy is characterized by the formation of an autophagosome, a double-membrane structure which engulfs organelles or long-lived proteins and fuses with lysosomes. Microautophagy is defined by the direct incorporation of cytosolic content into a lysosome/vacuole by the invagination of its surface. Chaperone-mediated autophagy involves the direct translocation of proteins into lysosomes in a 70 kDa heat-shock cognate protein–mediated manner. The machinery of macroautophagy is fairly well understood, whereas that of microautophagy has not yet been fully elucidated in mammals. The process of macroautophagy proceeds in multiple sequential steps: initiation and nucleation of isolation membranes, elongation of phagophores and engulfment of organelles or long-lived proteins, docking and fusion of phagophores (autophagosome formation), fusion of autophagosomes with lysosomes, and lysosomal degradation of cargos. Although autophagy has been regarded as a nonselective process, accumulating lines of evidence indicate the existence of selective autophagy, through which damaged organelles, such as mitochondria, endoplasmic reticulum, ribosomes, and peroxisomes, are selectively degraded. This selective autophagy is collectively called organelle-specific autophagy.15,16

Recent investigations have unveiled defined molecular mechanisms and the functions of organelle-specific autophagy. Among them, mitochondria-specific autophagy, termed mitophagy, has been most intensively investigated. Here, we discuss the current understanding of the molecular mechanisms mediating mitophagy and the role of mitophagy in mediating physiological and pathological functions in the heart.

What Is Organelle-Specific Autophagy?

The existence of a selective autophagic process for organelles was first proposed for the endoplasmic reticulum in 1973.17,18 Since then, molecular mechanisms mediating the organelle-specific autophagy in the endoplasmic reticulum (endoplasmic reticulum–phagy/reticulophagy), peroxisomes (pexophagy), ribosomes (ribophagy), and mitochondria (mitophagy) have been investigated in yeast.19-29 Both macroautophagy and microautophagy play a role in pexophagy and are termed macropexophagy and micropexophagy, respectively.19,21,24,28,30 Because microautophagy uses autophagy-related (Atg) proteins in yeast, it is hard to distinguish the particular contributions of microautophagy and macroautophagy to overall organelle-specific autophagy.30 Although some studies suggest a contribution of microautophagy to mitophagy, its contribution is largely unknown.31,32 Therefore, we hereafter use the term mitophagy to reference macro-mitophagy.

Yeast peroxisomes were ideal organelles for the initial studies of selective autophagy.21 Macropexophagy eliminates redundant or inactive peroxisomes without acceleration of autophagic degradation of other organelles;21 although peroxisomes can be degraded nonspecifically, the specific process also takes place under certain conditions, and the term pexophagy was generally accepted by researchers.18,19 Some labeling proteins localized in the peroxisome were later identified, such as peroxisomal membrane anchor protein PEX14, Atg30, and Atg37, which are essential for macropexophagy.20,28,33 The phosphorylation of Atg30 is essential for its interaction with Atg8 and Atg11, which is followed by macropexophagy.28,33,34

The term mitophagy was first introduced by Lemasters in 2005 to describe the selective autophagy of mitochondria and emphasize the nonrandom nature of the process in yeast after the identification of SUN family protein UTH1.9 This term had been widely accepted without enough evidence for its selectivity at the beginning.18 The molecular basis of mitophagy has since been first investigated in yeast. Most importantly, mitochondrial-targeted proteins, such as SUN family protein UTH1, Aup1p, and Atg32, which mark damaged mitochondria and subject them to autophagic removal, have been identified in yeast.24,25,35,36 Atg32 accumulates in the outer membrane of mitochondria (OMM) in response to starvation or in the post-log phase.21,25 Atg32 interacts with Atg8 (Figure 1).24,25 After phosphorylation of Atg32 at serine (Ser) 114 and 119 by casein kinase 2 (CK2), the N-terminus of Atg32 binds to the C-terminus of Atg11 (Figure 1).26 Subsequently, Atg11, which connects to dynamin-related GTPase DNM1, a mitochondrial fission protein, recruits the fission complex to mitochondria, a step that is essential for mitophagy (Figure 1).37
Although knowledge obtained from yeast has served as a useful resource for elucidating the mechanism of mitophagy in mammalian cells, the metabolic processes during the induction of mitophagy are distinct between yeast and mammalian cells. Saccharomyces cerevisiae, a budding yeast, prefers using the glycolytic pathway even when oxygen is abundant.38 When glucose is exhausted, a diauxic shift takes place and yeast start to use mitochondrial oxidative respiratory phosphorylation.39 On the other hand, mammalian cells primarily use mitochondrial oxidative phosphorylation in the presence of oxygen. Thus, induction of mitophagy in yeast and mammalian cells may be distinct in terms of functional significance and mechanism of activation.

In yeast, vacuoles containing mitochondria alone but no other organelles can be observed frequently through electron microscopic analyses. Yeast strains lacking mitophagy still use mitochondrial oxidative respiratory phosphorylation.40 On the other hand, mammalian cells primarily use mitochondrial oxidative phosphorylation in the presence of oxygen. Thus, induction of mitophagy in yeast and mammalian cells may be distinct in terms of functional significance and mechanism of activation.

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biomarkers. For example, accumulation of damaged mitochondria can also be demonstrated by increases in the mitochondrial mass, which can be evaluated by isolating mitochondria and determining their content relative to the starting tissue or cell preparation, or by increases in mitochondrial content, which is estimated by determining the relative ratios of mitochondrial biomarkers, including citrate synthase activity, cardiolipin content, and complex I-IV proteins, to cytosolic proteins. Mitochondrial swelling assays are used to show increased sensitivity of the mitochondrial permeability transition pore to Ca\(^{2+}\). The mitochondrial membrane potential is often depolarized, and this can be monitored using JC-1, TMRE, or TMRM. Mitochondrial respiration can be evaluated with measurement of the time-dependent oxygen consumption using Clarke electrodes, and the activity of the electron transport chain can be monitored with biochemical analyses of freshly prepared mitochondrial fractions.

At present, there is no single experimental method sufficient for the assessment of mitochondrial autophagy because none of these assays alone can prove the presence of cargo-specific autophagy, such as mitophagy. Caution should be exercised when interpreting the results obtained from these assays. If more information regarding how mitophagy is induced becomes available in the future, the mechanism can be traced as an indicator of mitophagy, and loss-of-function approaches can be taken to show the specific involvement of mitophagy. Currently, Parkinson juvenile disease protein 2 (Parkin) translocation to mitochondria and Parkin-dependent ubiquitination of mitochondrial proteins (See below) are often used to show activation of mitophagy. However, whether this mechanism represents the major mechanism of mitochondrial autophagy in the presence of a given stress in the heart requires further investigation.

**Molecular Mechanisms Mediating Mitophagy**

Most of the studies conducted thus far have focused on the molecular mechanism by which damaged mitochondria are recognized and engulfed by autophagosomes. In the case of mitophagy in yeast, Atg32 labels damaged mitochondria and recruits phagophores by acting as a receptor for Atg8 through its Atg8 family interacting motif. In the case of mammalian cells, Mitochondrial proteases and peptidases continuously degrade Pink1 in intact mitochondria. However, Pink1 is not imported to the inner membrane and is not cleaved in depolarized mitochondria. Pink1 then accumulates at the outer membrane and recruits Parkin. Mfn2 phosphorylated by Pink1 acts as a receptor for Parkin on mitochondria. Parkin ubiquitinates multiple proteins of the outer membrane. These ubiquitinated proteins are recognized by p62, a ubiquitin- and microtubule-associated protein 1 light chain 3 (LC3)-binding adaptor protein, followed by mitochondrial autophagy.

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**Figure 1. The mechanism of mitophagy in yeast.** Casein kinase 2 (CK2) directly phosphorylates autophagy-related protein (Atg)32 at serine (Ser) 114 and Ser 119 when cells are cultured in lactate medium and then shifted to nitrogen starvation medium supplemented with glucose. This phosphorylation, especially phosphorylation at Ser 114, is critically important for the Atg32–Atg11 interaction, which is required for the delivery of mitochondria to the phagophore assembly site (PAS). Atg11 recruits the mitochondrial fission complex, which consists of dynamin-related GTPase Dnm1 (Dnm1), fission 1 (Fis1), Mdv1, and Caf4. Subsequently, mitochondrial fission and mitophagy take place. Mitochondrial division is important for mitophagy in yeast.

**Figure 2. Microtubule-associated protein 1 light chain 3 (LC3)–interacting molecules act as receptors for autophagosomes on mitochondria.** A, B, Nix and Bnip3, BH3-only proteins, interact with LC3 through the LC3-interacting region (LIR) and regulate mitochondrial autophagy. Oxidative stress induces homodimerization and activation of Bnip3. Phosphorylation of the LIR in Bnip3 promotes the association between Bnip3 and LC3. C, Under hypoxia, dephosphorylation of FUNDC1 at Ser 13 or tyrosine (Tyr) 18 stabilizes the interaction between FUNDC1 and LC3. D, Cardiolipin, a phospholipid of the IMM, translocates to the mitochondrial surface in response to mitochondrial damage. The externalized cardiolipin binds to LC3.

**Figure 3. The mechanism of mitochondrial autophagy mediated by PTEN-inducible putative kinase 1 (Pink1)–Parkinson juvenile disease protein 2 (Parkin) in mammalian cells.** Mitochondrial proteases and peptidases continuously degrade Pink1 in intact mitochondria. However, Pink1 is not imported to the inner membrane and is not cleaved in depolarized mitochondria. Pink1 then accumulates at the outer membrane and recruits Parkin. Mfn2 phosphorylated by Pink1 acts as a receptor for Parkin on mitochondria. Parkin ubiquitinates multiple proteins of the outer membrane. These ubiquitinated proteins are recognized by p62, a ubiquitin- and microtubule-associated protein 1 light chain 3 (LC3)-binding adaptor protein, followed by mitochondrial autophagy.
cells, the process seems more complex, and there are several ways for damaged mitochondria to be recognized by phagophores. As in yeast, one mechanism uses either proteins or lipids on the mitochondrial membrane as receptors for LC3. To date, a mammalian homolog of Atg32 has not been reported. As introduced further, however, NIP3-like protein X (Nix/Bnip3L), BCL2/adenovirus E1B 19kDa interacting protein 3 (Bnip3), FUN14 domain containing 1 (FUNDC1), and Cardiolipin function as receptors for LC3 (Figure 2).\(^{53-57}\) Another mechanism uses ubiquitination of mitochondrial proteins followed by interaction with the adaptor proteins connecting ubiquitin with LC3. The representative case is the PTEN-inducible putative kinase 1 (Pink1)–Parkin pathway for the ubiquitination of mitochondrial proteins, with sequestosome 1 (p62) and neighbor of BRCA1 gene 1 acting as adaptor proteins (Figure 3).\(^{58,59}\) In addition, CK2, which phosphorylates Atg32 in yeast, has been reported to phosphorylate p62 at Ser 403, and this phosphorylation increases the affinity between its ubiquitin-associated domain and polyubiquitination chains on mitochondrial proteins in mammalian cells.\(^{60}\) However, the involvement of this machinery in mitochondrial autophagy has not yet been validated.\(^{60}\) The roles of key molecules in mediating mitophagy are discussed below.

**Pink1, Parkin, and p62**

Pink1- and Parkin-mediated mitochondrial autophagy is currently the most well established mechanism mediating mitophagy in mammalian cells.\(^{61}\) Both Pink1 and Parkin are linked to the pathogenesis of autosomal recessive juvenile Parkinsonism.\(^{62}\) Pink1 is a serine/threonine kinase that has a mitochondria-targeting signal in its N-terminus.\(^{63}\) After import into mitochondria through translocase of outer membrane and translocase of inner membrane complexes, Pink1 is anchored at the IMM.\(^{64}\) In intact mitochondria, matrix processing peptidase and presenilin-associated rhomboid-like continuously degrade Pink1.\(^{65,66}\) However, in depolarized mitochondria, the import to the IMM is inhibited and Pink1 accumulates at the OMM. Pink1 then forms a 700 kDa complex with translocase of outer membrane and undergoes autophosphorylation at Ser 228 and Ser 402.\(^{66,67}\) Pink1 is also accumulated on the OMM in response to an increase in unfolded proteins in mitochondria, thereby playing an essential role in mediating mitophagic removal of polarized mitochondria.\(^{68}\) Activated Pink1 recruits Parkin, a cytosolic E3 ubiquitin ligase, to damaged mitochondria and promotes their degradation through phosphorylation of multiple substrates. Pink1 phosphorylates Mfn2, which in turn acts as a mitochondrial receptor for Parkin in cardiomyocytes.\(^{69}\) A defect in Parkin translocation was observed in Mfn2-deficient neurons,\(^{70}\) suggesting that Mfn2 plays a critical role in recruiting Parkin to mitochondria in multiple cell types. However, it should be noted that the translocation of Parkin to mitochondria can still be observed in mouse embryonic fibroblasts lacking Mfn1 and Mfn2, suggesting the existence of an alternative or compensatory mechanism for recruiting Parkin.\(^{71}\) Stable expression of Pink1 anchored to the outer membrane can induce mitochondrial accumulation of Parkin, followed by mitochondrial autophagy in a manner independent of membrane potential.\(^{64}\) Ectopic expression of Pink1 in peroxisomes recruits Parkin to peroxisomes, accompanied by ubiquitination and selective autophagic clearance of peroxisomes.\(^{66}\) These results suggest that Pink1 acts downstream or independently of mitochondrial depolarization. Although initial studies suggested that Pink1 phosphorylates Parkin in its ubiquitin-like domain, thereby stimulating the E3 ligase activity of Parkin,\(^{72,73}\) mutations of conserved serine/threonine residues in Parkin do not completely suppress its activity, suggesting that Pink1 has additional substrates through which it activates Parkin. In fact, Pink1 phosphorylates ubiquitin conjugated to mitochondrial proteins at Ser 65,\(^{74,76}\) which in turn directly activates Parkin and promotes further ubiquitination of mitochondrial proteins.\(^{77}\) Multiple mitochondrial proteins, including voltage-dependent anion channel, Mfn1/2, translocase of outer membrane, fission 1, ras homolog family member T1/2, and mitochondrial hexokinase, have been identified as substrates of Parkin.\(^{66,78-80}\) It has been shown that Parkin-labeled mitochondria are removed by autophagy bit-by-bit, which occurs where Parkin-labeled mitochondria and endoplasmic reticulum intersect.\(^{71}\) Polyubiquitination catalyzed by Parkin leads to recruitment of p62, a ubiquitin- and LC3-binding adaptor protein, followed by perinuclear clustering of damaged mitochondria.\(^{59,78,82,83}\) However, whether p62 is essential for Parkin-mediated mitochondrial autophagy is controversial.\(^{59,82,83}\) Although degradation of the IMM and matrix proteins occurs through mitochondrial autophagy, degradation of OMM proteins can take place also through a proteasome-dependent mechanism mediated by Parkin.\(^{46}\) Parkin promotes recruitment of the AAA ATPase valosin containing protein, which extracts ubiquitinated proteins for proteasomal degradation, to damaged mitochondria.\(^{46}\) Parkin and Pink1 are also involved in the removal of damaged mitochondria through a vesicular trafficking pathway in which mitochondria-derived vesicles containing mitochondrial proteins are transported to lysosomes for degradation.\(^{85-87}\) These findings account for the difficulty in distinguishing typical mitochondrial autophagy from other forms of mitochondrial protein degradation based on Pink1–Parkin dependency alone.

Pink1–Parkin-mediated mitophagy is negatively regulated by USP30, a deubiquitinase localized in the OMM, by removing ubiquitin from substrates ubiquitinated by Parkin\(^{88}\) and Clec16a, a membrane-associated endosomal protein which promotes proteasomal degradation of Parkin through Nrdp1, another E3 ubiquitin ligase. Tumor protein p53 (p53) inhibits mitophagy by sequestering Parkin in the cytosol,\(^{89}\) whereas b-cell leukemia/lymphoma 2 protein (Bcl-2) family proteins, including Bcl-xL, MCL-1, and Bcl-2, on the OMM, inhibit mitophagy through inhibition of Parkin translocation to depolarized mitochondria.\(^{90}\)

Besides mitophagy and the mitochondria-derived vesicles pathway, Parkin and Pink1 also affect the quality control of mitochondria through several other mechanisms.\(^{62}\) For example, Parkin and Pink1 affect mitochondrial motility through Pink1-mediated phosphorylation and Parkin-mediated proteasomal degradation of Miro, an OMM protein involved in mitochondrial trafficking. Stabilization of Pink1 and Parkin activation immobilize damaged mitochondria through degradation of Miro, which in turn facilitates the removal of damaged mitochondria through mitophagy.\(^{91}\) Parkin positively
regulates mitochondrial biogenesis through proteasomal degradation of PARIS, a zinc-finger protein, which suppresses transcription of peroxisome proliferator–activated receptor-gamma coactivator-1α, a positive regulator of mitochondrial biogenesis.52 Parkin also regulates fat uptake by controlling the stability of CD36 through ubiquitination in hepatocytes.53 These studies suggest that Parkin contributes in diverse ways to mitochondrial quality control and metabolism.

Although many molecules of the autophagic machinery were discovered in yeast, p62 is absent in lower eukaryotes.94 Recently, Lu et al discovered CUE (coupling of ubiquitin endoplasmic reticulum degradation)-domain targeting proteins, a new class of ubiquitin-Atg8/LC3 adaptors.94 The CUE proteins are Cue5p in yeast and toll interacting protein in human.94 Although it differs in its domain arrangement, toll interacting protein fulfills both the biochemical and genetic criteria for being a functional human homolog of yeast Cue5p.94 These proteins interact with Atg8 (LC3) through Atg8 family interacting motif (also termed as LC3-interacting region [LIR]) and with ubiquitin through a CUE domain but not through a ubiquitin-associated domain like p62 or neighbor of BRCA1 gene 1.94 Toll interacting protein binds to ubiquitin conjugates more tightly than p62 and is more effective at clearing huntington poly-glutamine protein than p62.94 Toll interacting protein seems to specifically target highly aggregation-prone proteins for autophagy, but its role in organelle-selective autophagy has not yet been clarified.94

Nix/Bnip3L and Bnip3

To date, some mitochondria-labeling proteins, which also bind to LC3 or LC3 homologs through the LIR as a mitochondrial receptor for autophagosomes, have been identified in mammalian cells. Nix/Bnip3L and Bnip3 are included among these OMM proteins.53–55 They are BH3-only proteins and proapoptotic members of the Bcl-2 family.95–96 The protein level of Nix/Bnip3L is increased in the final stage of erythroid maturation, and genetic ablation of Nix/Bnip3L prevents the loss of mitochondrial membrane potential and sequestration of mitochondria into autophagosomes.95 Treatment with carbonyl cyanide m-chlorophenyl hydrazine, an uncoupling chemical, or BH3 mimetic induces a loss of membrane potential and restores mitochondrial autophagy in Nix/Bnip3L−/− erythrocytes, suggesting that Nix/Bnip3L–mediated loss of membrane potential is important for mitochondrial autophagy.95 Nix/Bnip3L regulates Parkin translocation to mitochondria.96 Mutation of the LIR of Nix/Bnip3L results in a partial reduction of mitochondrial autophagy.57 Given that oxidized cardiolipin promotes the release of proapoptotic factors into the cytosol, Chu et al speculated that externalized cardiolipin undergoes oxidation and accelerates apoptosis in the event of unsuccessful clearance of damaged mitochondria.57

Kubli et al reported that oxidative stress-induced homodimerization of Bnip3 is observed after ischemia/reperfusion (I/R) in the heart and that this dimerization correlates with its activation.100 Bnip3 induces extensive fragmentation and autophagy of mitochondria in HL-1 cells, and this phenomenon is independent of mitochondrial permeability transition pore opening or of Bcl-2-associated X protein/Bcl-2-antagonist/killer 1.101,102 The mitochondrial fragmentation induced by Bnip3 occurs through its direct inhibition of optic atrophy 1 (Opa1), a fusion protein.103 Recent evidence showed that phosphorylation of the LIR in Bnip3 promotes the interaction between Bnip3 and LC3B, thereby inducing mitochondrial autophagy.104 However, the responsible kinase has not yet been identified. Nix and Bnip3 promote apoptosis of cardiomyocytes through stimulation of OMM permeabilization.105,106 Nix also promotes necrosis of cardiomyocytes by stimulating endoplasmic reticulum–mitochondria crosstalk, Ca2+ overload, and consequent mitochondrial permeability transition pore opening.107 Bnip3 also stimulates myocardial necrosis in response to doxorubicin treatment by disrupting formation of mitochondrial protein complexes between the key respiratory proteins.108 Thus, what determines the role of Bnip3 in promoting cell death or survival through mitochondrial autophagy remains to be elucidated in the heart.

**FUNDIC1**

FUNDIC1 is a mitochondrial outer membrane protein that integrates with LC3 through its LIR under hypoxic conditions.56 During starvation, mitochondrial clearance does not depend on FUNDIC1, suggesting that it is specific for hypoxia-induced mitochondrial autophagy.56 FUNDIC1 is expressed under normoxia; however, the interaction between FUNDIC1 and LC3 is stabilized under hypoxic conditions, which is attributable to dephosphorylation at tyrosine 18 during hypoxia. FUNDIC1 also acts as a mitochondrial receptor for unc-51-like autophagy activating kinase 1.109 unc-51-like autophagy activating kinase 1 translocates to depolarized mitochondria and phosphorylates FUNDIC1 at Ser 17, thereby promoting mitochondrial autophagy.109 Mitochondrially localized phosphorylcysteine mutase family member 5 phosphatase directly dephosphorylates FUNDIC1 at Ser 13 on hypoxia or carbonyl cyanide-p-trifluoromethoxyphenylhydrazone treatment.110 This dephosphorylation of FUNDIC1 promotes its interaction with LC3 and mitochondrial autophagy, whereas CK2 phosphorylates the same residue of FUNDIC1, thereby negatively regulating mitochondrial autophagy.110 CK2 phosphorylates Atg32 and promotes mitophagy in yeast. However, the effect of phosphorylation of FUNDIC1 is opposite to that of phosphorylation of Atg32.

**Cardiolipin**

Cardiolipin, a phospholipid of the IMM, has been reported to translocate to the OMM in response to mitochondrial injury and interact directly with LC3 in primary cortical neurons and SH-SY5Y cells.52 The inhibition of cardiolipin synthase or of phospholipid scramblase-3 reduces the delivery of mitochondria to autophagosomes.57 Mutation of the residues predicted to be cardiolipin interaction sites in LC3 inhibits mitochondrial autophagy.57 Given that oxidized cardiolipin promotes the release of proapoptotic factors into the cytosol, Chu et al speculated that externalized cardiolipin undergoes oxidation and accelerates apoptosis in the event of unsuccessful clearance of damaged mitochondria.57

Overexpression of acyl-CoA:monolysocardiolipin acyltransferase, an enzyme that catalyzes pathological remodeling of cardiolipin, stimulates oxidative stress and clearance of mitochondria via autophagy in H9c2 cells. ALCAT knockout mice show upregulation of Pimk1, and both oxidative stress and mitochondrial dysfunction in response to L-tyrosine-induced stress are attenuated in these mice. Whether cardiolipin
peroxidation directly affects mitochondrial autophagy or mitochondrial autophagy is regulated secondarily by mitochondrial dysfunction/oxidation remains to be elucidated.111

**General Control of Amino Acid Synthesis 5-Like 1**

Increasing lines of evidence suggest that lysine acetylation controls many cellular functions, including autophagy, in response to metabolic stress.112 Acetyl-CoA, an intermediate product of metabolic pathways whose acetyl moiety is transferred for protein acetylation, is a negative regulator autophagy.113 During starvation, the level of acetyl-CoA is thought to be diminished. In addition, general control of amino acid synthesis 5-like 1 (GCN5L1), a component of the mitochondrial acetyltransferase machinery, is downregulated, whereas sirtuin 3, a mitochondrial deacetylase, is activated in HepG2 cells.114 Downregulation of GCN5L1 diminishes acetylation of mitochondrial proteins and stimulates mitochondrial autophagy, which, in turn, slows down respiration and induces stress-resilience in cells.114 This mitochondrial autophagy is both Atg5- and p62-dependent but Parkin-independent, and thus, whether autophagy regulated by GCN5L1 is mitochondria-selective is currently unknown. One mechanism through which the reduced protein acetylation induces mitochondrial autophagy is stimulation of transcription factor EB, a master regulator of lysosomal biogenesis. Interestingly, peroxisome proliferator–activated receptor-gamma coactivator-1α, a key regulator of mitochondrial biogenesis, is upregulated in parallel, so that mitochondrial turnover is stimulated without diminishing the total number of mitochondria.115 Whether such a mechanism also exists in cardiomyocytes and, if so, when it is activated and to what extent it is involved in the clearance of damaged mitochondria in the heart remains to be elucidated. In theory, mitophagy and mitochondrial biogenesis should be coupled. If so, investigating the underlying mechanisms, particularly the role of transcription factor EB in regulating peroxisome proliferator–activated receptor-gamma coactivator-1α/β, NRF1/2 and Tfam, in cardiomyocytes is of great interest.

**Mitochondrial Fission and Fusion Proteins**

Mitochondria are highly dynamic organelles and their morphology changes continuously through fusion and fission.116 The fusion of mitochondria is regulated by Mfn1 and Mfn2 localized on the OMM and Opalp on the IMM, whereas fission is regulated by Drp1 (dynamin 1-like), fission 1, and Miff.117 Although dynamin-related GTPase DNLM1, a yeast homolog of mammalian Drp1, plays an important role in mediating mitophagy in yeast,118 whether fission is prerequisite for mitochondrial autophagy and, if so, how it is coupled to autophagy are not fully understood in mammalian cells.114 Twig et al reported that fission events often generate uneven daughter mitochondria and that the one with reduced membrane potential has a reduced probability to refuse in INS1 cells.11 The daughter mitochondria that are unable to refuse are characterized by decreased expression levels of Opalp. Inhibition of fission through a dominant negative form of Drp1 or knockdown of fission 1, a factor that is involved in recruiting Drp1 to mitochondria, inhibits mitochondrial autophagy and causes accumulation of dysfunctional mitochondria.11 This study suggests that mitochondrial fission is important to segregate dysfunctional mitochondrial for their removal through autophagy. Mouse embryonic fibroblast cells deficient in Opalp or Mfn1/2 exhibit an increase in fragmented mitochondria and mitochondrial autophagy during starvation, whereas downregulation of Drp1 induces unopposed fusion of mitochondria and prevents mitochondrial autophagy.119 Parkin promotes mitochondrial fission through ubiquitination and degradation of Mfn1 and Mfn2, which, in turn, leads to increases in mitophagy.120 Mild and transient oxidative stress induces mitophagy, but not nonselective autophagy, in a Drp1-dependent manner in HeLa cells,121 and overexpression of fission 1 stimulates mitochondrial fragmentation and mitophagy in mouse embryonic fibroblast cells.122 These results are all consistent with the notion that mitochondrial autophagy couples to mitochondrial fission. However, it is possible that interventions used to alter mitochondrial fission and fusion could also directly or indirectly affect mitochondrial autophagy independently of the fission and fusion.123 For example, Drp1 affects general autophagy through its interaction with Becl-xL in cardiomyocytes.124 Even if mitochondrial fission directly affects autophagy, the molecular mechanisms by which fission mediates mitochondrial autophagy remain to be elucidated.

Genetic manipulation of proteins involved in mitochondrial fission/fusion induces both morphological changes and functional impairment in mitochondria in cardiomyocytes. Mitochondrial fragmentation and autophagy induced by overexpression of Bnip3 were both inhibited in the presence of dominant negative Drp1 in adult ventricular cardiomyocytes.125 Python mutant mice, which have a single mutation in exon 11 of the Drpl gene, exhibit elongated mitochondria, suggesting impairment of mitochondrial fission.126 These mice show an ≈50% reduction in adenosine triphosphate level in the heart and develop dilated cardiomyopathy.126 Although basal cardiac function is impaired in cardiac-specific Drp1 KO mice, a consensus has not been reached as to whether removal of dysfunctional mitochondria by autophagy is reduced in these mice. Ikeda et al reported that genetic deletion of Drp1 suppresses both general autophagy and mitochondrial autophagy in the mouse heart in vivo.124 Kageyama et al reported that Drp1 is required for Parkin-independent mitochondrial autophagy in the heart and that Drp1 and Parkin act synergistically to promote mitochondrial homeostasis in the brain.124 On the other hand, Song et al showed that Drp1 ablation increases mitophagy and causes generalized loss of mitochondria.125

The role of mitochondrial fusion in regulating autophagy and cardiac function seems more complex. Although homozygous mutation of Opalp is embryonic lethal,128 heterozygous Opalp mice exhibit late onset of cardiomyopathy, with a reduced mtDNA copy number and mitochondrial dysfunction.128 Whether mitochondrial autophagy is enhanced in this model is unknown. Downregulation of Mfn1 increased the number of small, spherical mitochondria,129 whereas downregulation of Mfn2 increased pleiomorphic and enlarged mitochondria in cardiomyocytes.130 In both cases, the cardiomyocytes were protected against stress, although another report showed that downregulation of Mfn2...
induces mitochondrial dysfunction. Combined ablation of Mfn1 and Mfn2 in the adult heart induces mitochondrial fragmentation and respiratory dysfunction, resulting in dilated cardiomyopathy. Downregulation of Mfn2 inhibits Parkin-mediated mitophagy, whereas unopposed fission caused by either single or combined downregulation of Mfn1 and Mfn2 may positively affect nonselective autophagy. Thus, the overall effects of Mfn1/2 downregulation on mitochondrial clearance by autophagy is unclear. Furthermore, Bhandari et al demonstrated that suppression of mitochondrial fusion rescues the cardiomyopathy induced by Parkin deficiency in Drosophila. These studies indicate that mitochondrial fusion contributes to the cardiac dysfunction of Parkin deficiency by promoting contamination of the healthy mitochondrial pool with damaged mitochondria, independently of mitophagy.

**Atypical Forms of Mitochondrial Clearance**

Macroautophagy is separated into several specific steps, including induction, recognition, and selection of cytoplasmic substrates, formation of the autophagosome around substrates, autophagosome–lysosome fusion, degradation of the autolysosomal contents, and release of the degradation products into the cytoplasm. The canonical, or conventional, autophagic pathway consists of evolutionarily conserved signaling molecules encoded by Atgs, including Atg4, Atg5, Beclin1 (Atg6), Atg7, Atg12, and Atg16, that govern these steps. On the other hand, increasing lines of evidence suggest that noncanonical autophagic pathways may also be present. Nishida et al revealed that Atg5−/−Atg7−/− double-knockout cells are still able to form autophagosomes and degrade autophagic substrates inside autolysosomes in response to certain stimuli. During this process of Atg5/Atg7-independent autophagy, termed alternative autophagy, lipidation of LC3 does not occur. Instead, Rab9, a small GTPase involved in membrane trafficking and fusion between the trans-Golgi network and late endosomes, plays a critical role in generating autophagosomes in the alternative autophagic pathway by promoting fusion of the phagophore with vesicles derived from the trans-Golgi network and late endosomes. Recent evidence suggests that unc-51 like autophagy activating kinase 1–dependent, Atg5-independent macroautophagy is the dominant process for removing mitochondria from reticulocytes in the final stage of erythrocyte maturation. Oxidative stress induces a vesicular transport pathway that selectively removes mitochondrial proteins for delivery to the lysosomes in COS7 cells. This mechanism does not require mitochondrial depolarization and is independent of Atg5 and LC3, indicating that it is distinct from either autophagy or selective mitophagy. However, the functional significance of alternative autophagy has not yet been demonstrated in the heart. Although conventional macroautophagy is attenuated in Drp1 knockout (KO) mice, Parkin-mediated mitophagy may be stimulated. Thus, it is possible that multiple mechanisms may mediate degradation of damaged mitochondria.

**What Is the Role of Mitophagy or Mitochondrial Autophagy in the Heart at Baseline?**

Conditional cardiac-specific **atg** 5 KO mice, which serve as a loss-of-function model for general autophagy, develop cardiac dysfunction, suggesting that general autophagy plays an essential role in maintaining the physiological function of the adult heart at baseline. These mice exhibit accumulation of misfolded proteins and damaged organelles, including mitochondria, consistent with the notion that protein/organellar quality control mediated by autophagy is essential for the heart even under resting conditions. Interestingly, **beclin1**−/− mice, another loss-of-function model of autophagy, do not exhibit any significant baseline cardiac phenotype, despite the fact that stress-induced autophagy is significantly inhibited. The difference in baseline cardiac phenotype in these mice may be caused by a difference in the level or the timing of autophagy suppression. Atg5 and Beclin1 (Atg6) may regulate qualitatively different types of autophagy. It is also possible that the development of compensatory mechanisms may vary depending on which Atg is downregulated. Alternatively, the difference may be related to the fact that autophagy-related genes also mediate functions other than autophagy in cells. These issues represent the difficulty and limitations of elucidating the functional significance of mitochondrial autophagy or mitophagy in the heart using a single genetically altered mouse model.

The aforementioned studies suggest the importance of general autophagy in the maintenance of protein/organellar quality control and cardiac function at baseline. However, whether mitochondrial autophagy or mitophagy is critically involved in this process remains unknown. Although Parkin and Pink1 regulate multiple cellular functions besides mitophagy, their direct involvement in mitophagy means that loss-of-function studies of Parkin and Pink1 can provide valuable information regarding the functional involvement of Pink1–Parkin-mediated mitophagy in the heart. In fact, increasing lines of evidence suggest that Pink1–Parkin-mediated autophagy participates in mitochondrial quality control and the maintenance of cardiac function at baseline. Cardiomyocytes in which Bnip3 is overexpressed are able to eliminate damaged mitochondria through autophagy via a Parkin-dependent mechanism, indicating that Parkin-mediated mitochondrial autophagy exists in cardiomyocytes. Parkin knockout mice exhibit normal cardiac function at baseline, but their cardiomyocytes exhibit morphologically disorganized mitochondria with or without mitochondrial dysfunction. Interestingly, clearance of mitochondria by autophagy seems to be maintained at baseline in these mice. This may be as a result of a low rate of mitochondrial degradation by autophagy at baseline, compensation for the lack of Parkin E3 ligase activity by other E3 ligases, such as tumor necrosis factor–receptor-associated factor 2, or compensation by Parkin-independent mechanisms of autophagy, such as general autophagy. Song et al suggested that the lack of Parkin-mediated mitophagy in heart-specific Mfn2 KO mice is compensated for by activation of nonselective autophagy in cardiomyocytes, thereby allowing cardiomyocytes to maintain mitochondrial quality. This suggests that both mitophagy and general autophagy cooperatively participate in the removal of mitochondria in cardiomyocytes. Currently, molecular mechanisms by which mitochondria are degraded by Mfn2–Parkin–independent autophagy are unknown. However, it would be interesting to
Role of Mitophagy or Mitochondrial Autophagy in Protection Against Cardiac Stress

The protective effect of mitophagy and mitochondrial autophagy in the heart generally seems more prominent during stress. In response to myocardial infarction (MI), activation of autophagy is observed most prominently in the border zone during the subacute phase (1 week after MI), returning to normal during the chronic phase (3 weeks after MI). The autophagic vacuoles in the border zone are large and contain organelles, including degraded mitochondria. In contrast, autophagy with normal-sized autophagosomes is upregulated in the remote zone during the chronic phase. Enhancing autophagy with rapamycin 2 weeks after coronary ligation ameliorates cardiac dysfunction and maladaptive remodeling, whereas inhibition of autophagy with bafilomycin A1 worsens them. These observations imply the existence of multiple forms of autophagy and suggest that some of them may play a role in mediating the clearance of mitochondria in a phase-dependent fashion after MI. A study using beclin1−/− mice also showed that suppression of autophagy is detrimental during the chronic phase of MI. Hoshino et al reported that autophagy peaks during the acute phase of MI (several hours after coronary ligation) in the border zone, as evaluated with GFP-LC3 transgenic mice. In this model, mitochondrial autophagy, as indicated by the presence of autophagosomes containing mitochondria, also takes place during the same period. MI induced by permanent coronary artery ligation upregulates p3 and TP53-induced glycolysis and apoptosis regulator in mice. Genetic deletion of p53 or TP53-induced glycolysis and apoptosis regulator in mice stimulates mitochondrial autophagy and inhibits accumulation of damaged mitochondria and apoptosis, an effect which is abolished by chloroquine treatment. The authors suggest that the beneficial effects of the p53 or TP53-induced glycolysis and apoptosis regulator downregulation may be mediated by mitophagy. These results are consistent with the negative regulation of mitophagy by cytosolic p53. Translocation of Parkin to mitochondria and ubiquitination of mitochondrial proteins occur during the acute phase of MI, suggesting that Parkin-mediated mitophagy is stimulated.Taken together, these results suggest that either mitophagy or mitochondrial autophagy is stimulated in the heart during the chronic phase of cardiac remodeling and that they are protective for the heart.

During myocardial reperfusion after a period of myocardial ischemia, mitochondria generate ROS, initiating a feed-forward mechanism of oxidative stress, mitochondrial injury, and cell death. Selective elimination of damaged mitochondria by mitophagy or mitochondrial autophagy is predicted to protect cardiomyocytes during reperfusion. In fact, loss of Pink1 has been reported to increase the infarct size after I/R, although this study did not examine mitochondrial autophagy in the heart. Ischemic preconditioning (IPC) induces the translocation of Parkin to mitochondria, and the IPC-mediated cardioprotective effect is abolished in Parkin KO mice. The translocation of p62 to mitochondria is also impaired in these mice, suggesting that Parkin and p62 act together to induce mitochondrial autophagy in response to IPC. Whether the cardioprotective effect of IPC requires mitophagy rather than the mitophagy-independent functions of Parkin remains to be elucidated. If mitochondrial autophagy does mediate the effect of IPC, investigating how preactivated autophagy protects the heart against I/R may allow identification of novel modalities of cardioprotection. Myocardial I/R injury is exacerbated in cardiac-specific drp1−/− mice, in which mitochondrial fission and autophagy are both inhibited. Thus, suppression of mitophagy and mitochondrial autophagy seems to be detrimental during I/R. Because translocation of Drp1 from the cytosol to mitochondria is stimulated by I/R, enhancement of the quality control mechanism seems to be essential for minimizing myocardial injury during reperfusion. On the other hand, it has been shown previously that Beclin1 haploinsufficiency suppresses autophagy and inhibits I/R injury. Why haploinsufficiency of Drp1 and Beclin1 exhibit directionally opposite effects on I/R injury is currently unknown. However, one possibility is that Drp1 and Beclin1 may affect general autophagy and mitochondrial autophagy to different extents. Another, less attractive, possibility is that Drp1 and Beclin1...
differentially affect cellular functions other than autophagy. Further investigation is required to address this issue.

There are fewer publications addressing mitochondrial autophagy during pressure overload. However, the protein level of Pink1 is known to be decreased after transverse aortic constriction. Because Pink1-deficient mice develop age-dependent hypertrophy and cardiac dysfunction accompanied by mitochondrial dysfunction even without pressure overload, downregulation of Pink1 and consequent suppression of mitochondrial autophagy may be detrimental during pressure overload as well.

**Perspective**

In summary, the recent progress regarding molecular mechanisms of mitophagy, including how damaged mitochondria are recognized and how they are engulfed by autophagosomes, has greatly improved our understanding of quality control mechanisms in mitochondria. However, our knowledge regarding mitophagy in the heart and the cardiomyocytes therein is limited. First of all, whether mitochondria are degraded by mitophagy or general autophagy requires more studies, using more sensitive and accurate methods to monitor lysosomal degradation of mitochondrial proteins, together with electron microscopic observation to determine whether autophagosomes contain mitochondria alone or other materials as well. Establishing more reliable methods to monitor mitochondrial autophagy would dramatically advance our understanding of the molecular signaling mechanisms of mitophagy/mitochondrial autophagy. In particular, whether the Pink1/Parkin pathway is involved in mitochondrial autophagy/mitophagy in cardiomyocytes in response to relevant stresses in vivo urgently requires more investigation. If the Pink1/Parkin pathway does play an important role in mitophagy/mitochondrial autophagy in cardiomyocytes during relevant stresses, then more investigation is required regarding interactions between the Pink1/Parkin pathway, the receptor-mediated mechanisms, including those mediated by Bnip3, Nix, FUNDC, and cardiolipin, and the protein kinases, such as unc-51 like autophagy activating kinase 1/2, AMP (adenosine monophosphate)-activated protein kinase, mTOR, and CK2. In addition, we cannot exclude the presence of novel mechanisms. For example, it is possible that novel functional homologs of yeast Atg32 and Atg11 may exist. Unbiased approaches are therefore essential to clarify whether this can be caused by excessive mitochondrial autophagy or mitophagy and, if so, what would induce such a condition remain unknown.

Increasing lines of evidence suggest that autophagy is intimately involved in the survival and death of cardiomyocytes. It is likely that the beneficial effects of autophagy are partly mediated through elimination of damaged mitochondria and consequent prevention of mitochondrial dysfunction, oxidative stress, and cell death. To introduce modification of autophagy and mitophagy into the treatment of cardiovascular disease, further investigations are needed to better understand when autophagy is activated or inhibited and how it affects the function of mitochondria in response to a wide variety of cardiovascular stress conditions.

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None.

**References**


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