Biochimica et Biophysica Acta 1853 (2015) 2784–2790

Contents lists available at ScienceDirect

Biochimica et Biophysica Acta

journal homepage: www.elsevier.com/locate/bbamcr

Review

Selective removal of mitochondria via mitophagy: distinct pathways for different mitochondrial stresses☆

Huifang Wei [a,b], Lei Liu [a], Quan Chen [a,b,c,*]

[a] State Key Laboratory of Biomembrane and Membrane Biotechnology, Institute of Zoology, Chinese Academy of Sciences, Beijing 100101, China
[b] University of Chinese Academy of Sciences, Beijing 100049, China
[c] Tianjin Key Laboratory of Protein Science, College of Life Sciences, Nankai University, Tianjin 300071, China

ARTICLE INFO

Article history:
Received 28 January 2015
Received in revised form 17 March 2015
Accepted 25 March 2015
Available online 1 April 2015

Keywords:
Mitophagy
Mitophagy receptor
Atg32
FUNDC1
Parkin

ABSTRACT

The efficient and selective elimination of damaged or excessive mitochondria in response to bioenergetic and environmental cues is critical for maintaining a healthy and appropriate population of mitochondria. Mitophagy is considered to be the central mechanism of mitochondrial quality and quantity control. Atg32, a mitophagy receptor in yeast, recruits mitochondria targeted for degradation into the isolation membrane via both direct and indirect interactions with Atg8. In mammals, different mitophagy effectors, including the mitophagy receptors NIX, BNIP3 and FUDNC1 and the PINK1/Parkin pathway, have been identified to participate in the selective clearance of mitochondria. One common feature of mitophagy receptors is that they harbor an LC3-interacting region (LIR) that interacts with LC3, thus promoting the sequestration of mitochondria into the isolation membrane. Additionally, both receptor- and Parkin/PINK1-mediated mitophagy have been found to be regulated by reversible phosphorylation. Here, we review the recent progress in the understanding of the molecular mechanisms involved in selective mitophagy at multiple levels. We also discuss different mitophagy receptors from an evolutionary perspective and highlight the specific functions of and possible cooperation between distinct mechanisms of mitophagy. This article is part of a Special Issue entitled: Mitophagy.

1. Introduction

The term autophagy was coined by C. de Duve in 1963 to describe the lysosome-dependent degradation of cellular components, which is different from the clearance of endogenous proteins by the proteasome and from the endocytosis-mediated degradation of extracellular cargoes or cell membrane proteins [1,2]. Although autophagy was initially considered as a non-selective process, it is now widely accepted that autophagy can be induced in a highly selective manner [3,4]. Diverse cargoes such as protein aggregates, intracellular pathogens and damaged or excessive organelles, including mitochondria, can be removed via selective autophagy [5]. As multifunctional cellular organelles, mitochondria act as the cellular powerhouse, the metabolic center and the headquarters of apoptosis. Given that mitochondria are the primary source of reactive oxygen species (ROS), which are responsible for cellular oxidative damage, mitochondria can also exert potentially deleterious effects [6,7]. Moreover, the mass of mitochondria must match the varying needs of the cell in response to the bioenergetic and environmental changes [8,9]. As a result, the timely elimination of dysfunctional mitochondria and the preservation of an appropriate population of mitochondria are indispensible for normal cellular function and cell survival [8,10,11]. Mitochondrial quantity is maintained via mitochondrial biogenesis and the selective clearance of damaged or excessive organelles. Mitochondrial autophagy (or mitophagy) is thus considered to be the core mechanism of both mitochondrial quality and quantity control.

It has been nearly a decade since the term mitophagy was proposed to define the selective autophagy of mitochondria [10]. Recently, rapid progress has been made, and the underlying molecular mechanisms and (patho)physiological roles of mitophagy in development and diverse diseases have begun to be appreciated. Increasing evidence indicates the key role of mitophagy receptors, such as Atg32 in yeast [12,13] and NIX [14], BNIP3 [14] and FUNDC1 [15] in mammals, in the clearance of mitochondria. Moreover, PINK1/Parkin-mediated mitophagy appears to differ from receptor-mediated mitophagy, potentially via a ubiquitylation-related process for the selective removal of mitochondria that have lost their membrane potential [16]. It is interesting to note that mitophagy receptors on mitochondria appear to act as the common effectors in different mitophagy pathways, and FUNDC1 shares a series of features with Atg32.

☆ This article is part of a Special Issue entitled: Mitophagy.

* Corresponding author at: State Key Laboratory of Biomembrane and Membrane Biotechnology, Institute of Zoology, Chinese Academy of Sciences, Beijing 100101, China.
E-mail address: chenq@ioz.ac.cn (Q. Chen).

http://dx.doi.org/10.1016/j.bbamcr.2015.03.013
0167-4889/

2. Mitophagy in yeast: Atg32 as a mitophagy receptor

The knowledge that a molecular mechanism is involved in the selective elimination of mitochondria began with the identification of Uth1p in yeast. Primarily localized to the mitochondrial outer membrane, Uth1p is essential for the specific autophagic degradation of mitochondria in response to rapamycin treatment and nutrient deprivation [17]. In addition to Uth1p, Aup1p, a *Saccharomyces cerevisiae* PP1K ortholog localized to the mitochondrial intermembrane space, is required for efficient mitophagy in stationary phase cells [18]. Furthermore, the absence or mutation of the mitochondrial proteins Fmc1 [19], Mdm38 [20] and Mip1 [21] induce mitophagy; Yme1, a mitochondrial i-AAA (ATPases associated with diverse cellular activities in the intermembrane space) protease, has also been reported to play a controversial role in mitophagy [22–24]. A genetic screen for yeast mutants defective in mitophagy revealed that Atg33 might participate in the clearance of damaged mitochondria, although its functional mechanism remains to be explored [25,26] (Fig. 1).

As a breakthrough finding, two independent groups identified Atg32 as a mitophagy receptor in yeast based on genome-wide screen [12,13,25], which provides key insight into the mechanism of mitophagy in yeast. Similar to Uth1p and Aup1p, Atg32 is necessary for mitophagy but not for non-specific autophagy [12]. Atg32 is a 59 kDa protein localized to the outer mitochondrial membrane that contains one predicted transmembrane domain; its N and C terminals face the cytosol and the mitochondrial intermembrane space, respectively [12,13]. Atg32 mediates mitophagy via its interaction with Atg8 (the mammalian homolog of LC3) and Atg11 [13,22]. The cytosolic domain of Atg32 contains a W^{86}QAI motif, which serves as an Atg8 family interacting motif (AIM) and is crucial for the binding of Atg32 to Atg8 [13,22]. Mutations at Trp86 and Ile89 of the W^{86}QAI motif reduce the binding of Atg32 to Atg8, resulting in a partial mitophagy defect [13]. Atg32 also contains a consensus I^{112}/VLS motif, which is important for its binding to Atg11 [27]. Atg11 is a selective autophagy receptor that can recruit a range of cargoes to autophagosomes via its interaction with Atg8 [28]. An alanine substitution at Ser114 in the I/VLS motif affects Atg32 phosphorylation (see below) and strongly impairs mitophagy [27]. Thus, Atg32 has been proposed to recruit mitochondria to be sequestered into autophagosomes via direct or indirect interaction with Atg8.

The regulatory mechanism of Atg32-mediated mitophagy has recently been described. Okamoto et al. found that Atg32 is temporally unregulated prior to mitophagy under respiratory conditions and is subsequently degraded via autophagy-dependent and autophagy-independent processes [13]. The antioxidant compound N-acetylcysteine (NAC) inhibits mitophagy, presumably by suppressing Atg32 expression [13]. However, since NAC can suppress mitophagy by augmenting the cellular glutathione (GSH) pool rather than by scavenging ROS [29], the exact role of oxidative stress in Atg32-mediated mitophagy remains to be clarified.

Post-translational modification plays a key role in the regulation of Atg32-mediated mitophagy. Yoshimasa et al. found that Ser114 and Ser119 of Atg32 are phosphorylated under mitophagy-inducing conditions [27]. The phosphorylation of Atg32, especially at Ser114, subsequently mediates the Atg11–Atg32 interaction and mitophagy [27]. Another study identified Casein kinase 2(CK2) as a putative mediator of Atg32 phosphorylation at Ser114 and Ser119 based on a screen of kinase-deleted yeast strains [30]. The CK2-dependent phosphorylation of Atg32 stabilizes the Atg32–Atg11 interaction, thus promoting mitophagy; alternatively, the inhibition of CK2 specifically blocks mitophagy but not macroautophagy, pexophagy (the selective autophagy of peroxisomes) or the cytoplasm to vacuole targeting (Cvt) pathway [30]. These results suggest a specific regulatory role of CK2 in Atg32-mediated mitophagy. In addition to CK2, the Atg1 signaling pathway [22] and two mitogen-activated protein kinase (MAPK) pathways, Hog1-Pbs2 and Slt2 [27,31], have been reported to be involved in the induction of yeast mitophagy, but mechanism underlying these activities requires further investigation (Fig. 1). It also remains to be explored whether the several serine residues near the AIM of Atg32 are susceptible to phosphorylation, which might contribute to the regulation of the Atg32–Atg8 interaction and mitophagy progression. In addition, further studies are needed to determine whether mitophagy resulting from the loss of genes (Fmc1, Mdm38 or Mip1) is dependent on Atg32.

3. Mitophagy in mammalian systems

3.1. PINK1/Parkin-mediated mitophagy

Mutations of PINK1 and Parkin have been proposed to be the most common cause of recessive familial Parkinson's disease [32–34]. PTEN-

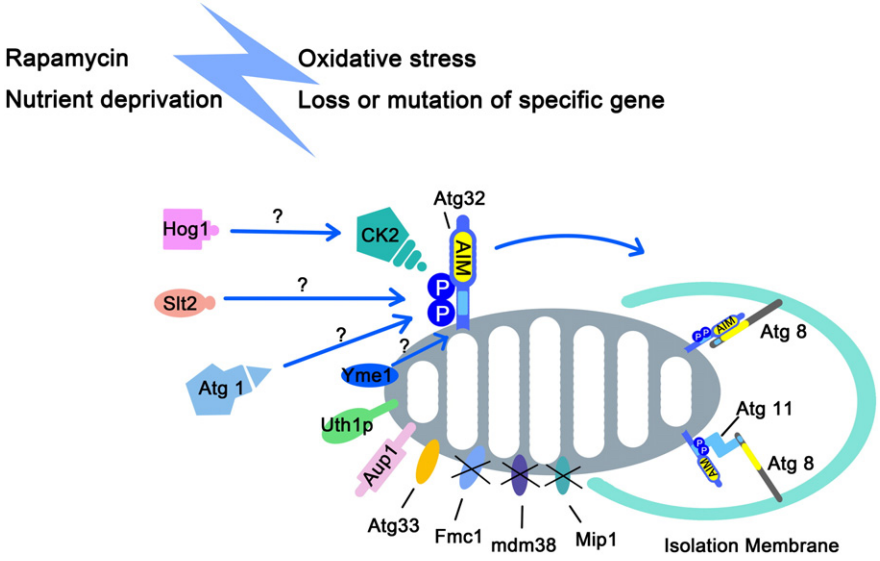

Fig. 1. Mechanism of mitophagy in yeast. Atg32, a mitophagy receptor localized to the outer mitochondrial membrane, possesses an AIM and an Atg11-binding motif at its C terminal, through which Atg32 interacts with Atg8 directly or indirectly via the bridge Atg11. When mitophagy is induced, Ser114 and Ser117 of Atg32 are phosphorylated by CK2, thus promoting the Atg32–Atg11 interaction and mitophagy. Hog1 may act upstream of CK2 to contribute to the phosphorylation of Atg32. Moreover, signaling pathways involving other kinases, such as Atg1, Pbs2 and Slt2, are required for mitophagy. Several other proteins, specifically Uth1p, Aup1, Yme1 and Atg33, have been reported to function in mitophagy. The loss or mutation of several mitochondrial proteins, including Fmc1, mdm38 and Mip1, can trigger mitophagy via an unknown mechanism.

induced putative kinase 1 (PINK1) is a nuclear-coded mitochondrial serine/threonine kinase [34], and Parkin is a cytosolic E3 ubiquitin ligase [35,36]. Genetic studies revealed that PINK1 and Parkin function in the same pathway and that PINK1 acts upstream of Parkin [37–39]. Extensive work during the past several years has greatly contributed to the partial elucidation of the molecular mechanism by which PINK1 and Parkin act together to mediate mitophagy in mammalian cells. It has been proposed that PINK1 functions as a mitochondrial stress sensor via its import and degradation, which is dependent on the mitochondrial membrane potential. In healthy mitochondria, PINK1 is imported into mitochondria and then rapidly undergoes cleavage and degradation at the inner mitochondrial membrane [40,41]. However, when the mitochondrial membrane potential is dissipated, PINK1 is stabilized on the outer mitochondrial membrane, where it recruits Parkin to damaged mitochondria [42–44] (Fig. 2). Recently, further details regarding the PINK1–Parkin interaction and the activation of Parkin have been revealed. It was found that PINK1 is activated following mitochondrial depolarization and undergoes phosphorylation at multiple sites, including Thr257, which enables PINK1 to phosphorylate Parkin at Ser65 and leads to the activation of the E3 ligase activity of Parkin [45] (Fig. 2). Furthermore, several independent studies have demonstrated that PINK1 phosphorylates ubiquitin at Ser65 and phosphorylated ubiquitin activates Parkin [46–48].

It is hypothesized that after Parkin is recruited to mitochondria and is subsequently activated, it ubiquitinates diverse mitochondrial outer membrane proteins, which may mediate the subsequent sequestration of mitochondria into the isolation membrane via an interaction with adaptor proteins (such as p62 and NRB1) on the isolation membrane. To date, investigators have identified several potential substrates of Parkin, such as mitofusins (Mfn1/2) [49], Miro [50], TOM70 [16], Drp1 [51] and PARIS (ZNF746) [52], further suggesting an extensive role of Parkin in mitochondrial dynamics, mitochondrial transport and the regulation of mitochondrial biogenesis. However, the specific role of these ubiquitinated outer mitochondrial membrane proteins in PINK1/Parkin-mediated mitophagy is poorly understood. Moreover, studies have shown that p62 is recruited to mitochondria together with Parkin, however,other investigations have suggested that p62 is unnecessary for the elimination of damaged mitochondria, challenging the role of this adaptor in the Pink1/Parkin pathway [53–55]. A recent study reported that Mfn2, which is phosphorylated by PINK1 and subsequently ubiquitinated by Parkin, appears to function as a receptor for Parkin and is required for the translocation of Parkin to damaged mitochondria [56]. Subsequently, optineurin, an autophagy receptor possessing both an ubiquitin-binding domain and an LIR (LC3-interacting region) motif, was identified to be a mitophagy receptor in the PINK1/Parkin pathway [57]. It was demonstrated that optineurin is recruited to damaged mitochondria via its association with ubiquitinated outer mitochondrial membrane proteins in a Parkin-dependent manner and subsequently induces the sequestration of mitochondria by autophagosomes via its interaction with LC3 in a p62-independent manner [57] (Fig. 2).

3.2. BNIP3 and NIX/BNIP3L in mammalian mitophagy

BCL2 and adenovirus E1B 19-kDa-interacting protein 3 (BNIP3) and BNIP3-like (BNIP3L, also known as NIX) are mitochondria-localized proteins that are related to the BH3-only family. In addition to their roles in cell death, both BNIP3 and NIX are found to interact with LC3 family proteins via their LIR motifs facing the cytosol, thereby mediating the clearance of mitochondria [14,58–60]. Studies using NIX −/− mice revealed that NIX is involved in the process of reticulocytes maturation [14,59,61,62]. In addition to NIX, other key effectors in the autophagy pathway, such as Atg7 and Ulk1, contribute to the clearance of mitochondria in reticulocytes [63,64]. Interestingly, Ulk1-dependent and Atg5-independent macroautophagy has been discovered to play a key role in mitochondrial clearance in reticulocytes [65,66]. It should also be noted that a non-autophagic mechanism may contribute to mitochondrial clearance during reticulocytes maturation [67].

The signaling events upstream of NIX/BNIP3-mediated mitophagy remain largely unknown. The existing evidence indicates that the upregulation of NIX/BNIP3 may be a crucial event that promotes their activity in mitophagy [59,63,68–70]. Interestingly, a recent study identified Ser17 and Ser24 as phosphorylation sites of BNIP3 that are responsible for enhancing the BNIP3–LC3 interaction [71], suggesting a possible role of kinase(s) or phosphatase(s) in the NIX phosphorylation-mediated regulation of mitophagy.

3.3. FUNDC1-mediated mitophagy

Recently, we have identified FUN14 domain-containing protein 1(FUNDC1) as a novel mitophagy receptor [15]. FUNDC1 is an outer mitochondrial membrane protein containing three transmembrane domains, and with its N-terminal and C-terminal region exposed to the cytosol and the intermembrane space, respectively [15]. In FUNDC1-silenced cells, hypoxia treatment fails to induce mitophagy compared to control cells, and mitophagy can be rescued by re-expressing wild-

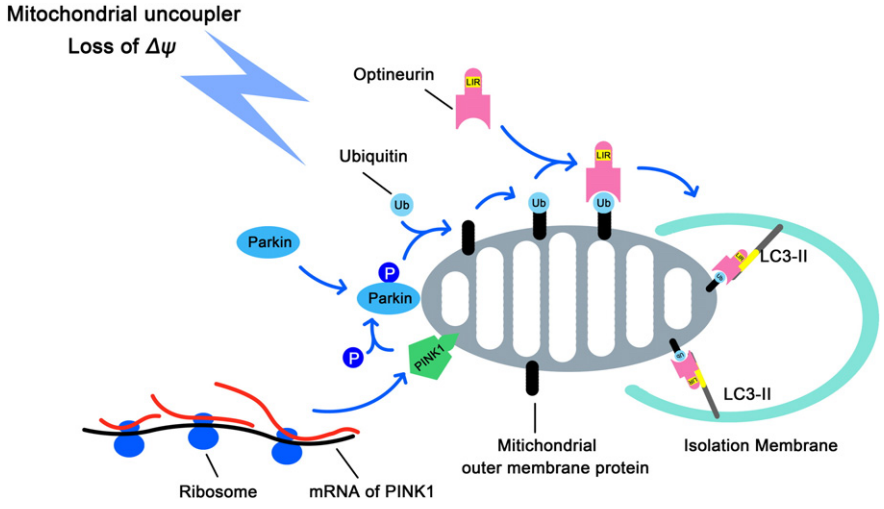

Fig. 2. Regulatory mechanism of PINK1/Parkin-mediated mitophagy. When the mitochondrial membrane potential ($\Delta\psi$) is dissipated, PINK1 is stabilized on mitochondria and then recruits Parkin to damaged mitochondria, resulting in the phosphorylation and activation of Parkin by PINK1. Then, Parkin ubiquitinates various outer mitochondrial membrane proteins. Optineurin associates with these ubiquitin tagged proteins and targets the isolation membrane to damaged mitochondria, leading to the autophagic clearance of mitochondria.

type FUNDC1 [15]. These results suggest that FUNDC1 functions as a specific mitophagy receptor during hypoxia-induced mitophagy.

3.3.1. Structure of FUNDC1

Atg8 homologs play an essential role in the elongation of the isolation membrane [72]. They are produced as pro-forms and then undergo cleavage into form I (such as LC3-I) by Atg4. Form I possesses a C-terminal glycine that can be conjugated to phosphatidylethanolamine on the membrane to produce form II (such as LC3-II) [72]. Thus, isolation membrane-anchored Atg8 homologs function as scaffolds to recruit various proteins (such as p62 [73,74], NBR1 [75] and optineurin [57,76]) to the isolation membrane. Molecular and structural studies have revealed that the interaction with Atg8 homologs is mediated by AIM or LIR. The consensus sequence for the core LIR motif is (W/F/Y)XX(L/I/V), which is often surrounded by one or more acidic residues [77]. We found that FUNDC1 harbors a LIR, Y^{18}EVL, in its cytosol-exposed N-terminal, and the LIR motif is essential for the FUNDC1–LC3 interaction [15]. The mutation of the LIR of FUNDC1 significantly impairs mitophagy, and the deletion of its LIR blocks the induction of mitophagy. These findings indicate that the FUNDC1–LC3 interaction is required for FUNDC1-induced mitophagy.

The alignment of FUNDC1 homologs from yeast to human reveals an evolutionary conservation of the FUNDC1 LIR motif in vertebrates but not in yeast or Drosophila (Fig. 3). There are also several acidic residues, either Asp or Glu surrounding the core motif, are conserved in vertebrates (Fig. 3), suggesting an evolutionary conservation of the mitophagy-related function of FUNDC1. Interestingly, the LIR motif of NIX displays a similar conservation pattern to that of FUNDC1 [14], indicating that vertebrates may have developed multiple mitophagy receptors during evolution.

3.3.2. Post-translational modifications regulate FUNDC1-mediated mitophagy

The regulatory mechanism of FUNDC1-mediated mitophagy has recently been revealed. It was found that the multi-site phosphorylation of FUNDC1 plays a key role in the regulation of the FUNDC1–LC3 interaction (Fig. 4). We found that FUNDC1 undergoes phosphorylation under normoxia [15,78]. Under normal conditions, Src and CK2 are kinases responsible for the phosphorylation of FUNDC1 at Tyr18 and Ser13, respectively, and these phosphorylation events inhibit the interaction of FUNDC1 with LC3 [15,78]. During hypoxia or mitochondrial uncoupler treatment, Src and CK2 are inactivated, and the mitochondrial phosphatase PGAM5 interacts with and dephosphorylates FUNDC1 at Ser13; this modification enhances the FUNDC1–LC3 interaction, thus inducing the sequestration of mitochondria by the isolation membrane [15,78]. The inhibition of either of these two kinases, Src and CK2, is not sufficient to activate mitophagy, but the coordinate inactivation of both kinases efficiently activates mitophagy [78]. Furthermore, mitophagy is abrogated following the knockdown of PGAM5 or the introduction of a cell-permeable unphosphorylated peptide encompassing Ser13 and the LIR of FUNDC1 [78].

More recently, we have characterized the regulation of the PGAM5–FUNDC1 interaction by BCL-XL [79] (Fig. 4). BCL-XL interacts with and inhibits PGAM5 via its BH3 domain to prevent the dephosphorylation of FUNDC1 at Ser13 under normoxia. However, the degradation of BCL-XL during hypoxia leads to the release of PGAM5 and facilitates the subsequent dephosphorylation of FUNDC1 at Ser13, thereby initiating FUNDC1-mediated mitophagy [79]. Because BCL-XL functions in autophagy via its interaction with Beclin1 [80], our finding suggests a second specific role of BCL-XL in mitophagy.

In addition to CK2 and Src, the Atg1 homolog ULK1 has been shown to interact with and phosphorylate FUNDC1 at Ser17 during hypoxia or mitochondrial uncoupler treatment, and these events promote the FUNDC1–LC3 interaction and mitophagy [81]. Collectively, the phosphorylations of FUNDC1 at 3 different sites near its LIR are responsible for the regulation of mitophagy in response to hypoxia or mitochondrial uncouplers (Fig. 4).

3.3.3. Expressional regulation of FUNDC1

In addition to post-translational modification, FUNDC1 expression also contributes to the regulatory mechanism of mitophagy. Recently, it was found that microRNA-137 is down-regulated in response to hypoxia and that this microRNA targets the expression of NIX and FUNDC1 [70]. MicroRNA-137 inhibits mitophagy by reducing the expression of mitophagy receptors, thereby leading to the suppression of mitophagy receptor–LC3 interactions [70]. However, our previous study showed that similar to Atg32 [13], FUNDC1 is down-regulated during hypoxia-induced mitophagy [15]. Therefore, the mechanism by which FUNDC1 expression is regulated during mitophagy remains to be clarified.

3.3.4. Atg32 and FUNDC1—possible functional counterparts

As described above, different mitophagy receptors, specifically NIX, BNIP3L and FUNDC1 have been identified in mammals. Similar to Atg32, these proteins function in the sequestration of mitochondria by autophagosomes via their interaction with the Atg8 homolog LC3. It is rather interesting that Atg32 and FUNDC1 share some common features, especially with respect to phosphorylation/dephosphorylation events [Table 1]. CK2 regulates the phosphorylation of both Atg32 in yeast and FUNDC1 in mammals. However, the phosphorylation of Atg32 by CK2 promotes mitophagy [30], whereas the FUNDC1–LC3 interaction is inhibited by CK2-mediated FUNDC1 phosphorylation under normal conditions [78]. Recent studies also revealed that Atg1 and its mammalian homolog ULK1 are involved in the regulation of Atg32 and FUNDC1, respectively (Table 1) [22,65]. In contrast to that of NIX and BNIP3, the function of both Atg32 and FUNDC1 appears to be regulated predominantly at the level of post-translational modifications rather than expression. Since the certain role of Atg1 and Hog1-Slt2 signaling pathway in Atg32-mediated mitophagy remains largely unknown, and the phosphatase targeting to Atg32 has yet to be identified, further investigations are warranted to solve these unanswered questions and will make a significant contribution to a full understanding of the evolution relationship between Atg32 and FUNDC1.

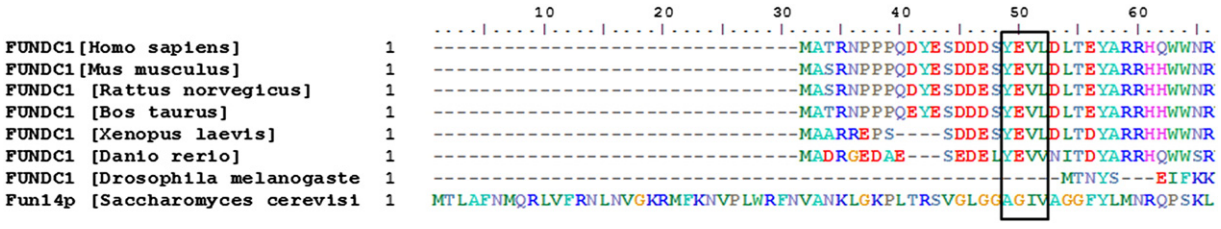

Fig. 3. Alignment of the LIR motifs of FUNDC1 from different species. The LIR motifs of FUNDC1 homologs from the indicated species were aligned using BioEdit software. The core LIR motifs are shown in the boxes.

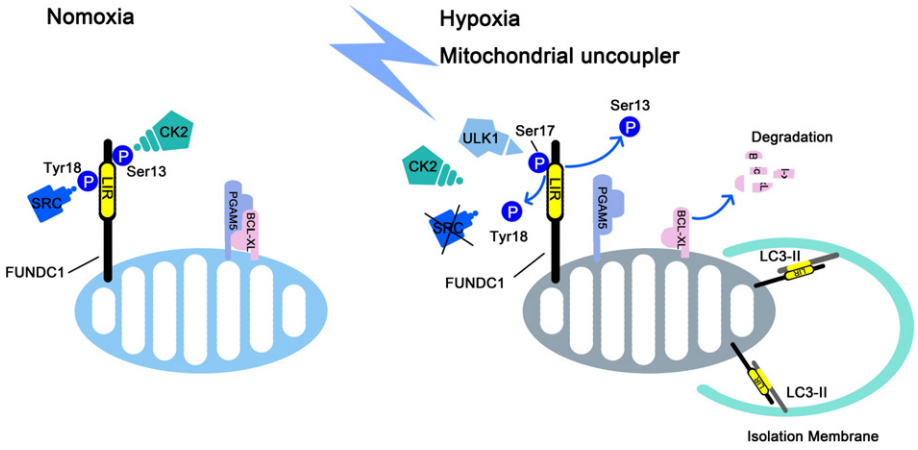

Fig. 4. Regulatory mechanism of FUNDC1-mediated mitophagy. Under normoxic conditions, two protein kinases, Src and CK2, phosphorylate FUNDC1 at Tyr18 and Ser13, respectively, thus inhibiting the FUNDC1–LC3 interaction and mitophagy. PGAM5 is blocked by BCL-XL under normoxia. In response to hypoxia or mitochondrial uncouplers, Src and CK2 are unable to phosphorylate FUNDC1, and PAGM5 is released, enabling the dephosphorylation of FUNDC1 at Ser13 to promote mitophagy. ULK1 also phosphorylates FUNDC1 at Ser17, which strengthens the FUNDC1–LC3 interaction.

4. Hypoxia and mitophagy

Hypoxia contributes to various physiological processes and is a characteristic of most solid tumors [82–84]. As the primary consumer of oxygen, mitochondria are undoubtedly influenced by hypoxia. Although there remains controversy regarding the impact of hypoxia on mitochondrial biogenesis, it has been well established that hypoxia can induce mitophagy [85]. It has been proposed that hypoxia-induced mitophagy is required to down-regulate oxidative phosphorylation to prevent ROS accumulation in a HIF-1α/BNIP3-dependent manner, which also requires the constitutive expression of Beclin-1 and Atg5 [86]. As mentioned above, both NIX and FUNDC1 have been reported to be involved in hypoxia-induced mitophagy, as the knockdown of either NIX or FUNDC1 leads to the significant impairment of mitophagy following hypoxia [70]. Thus, it is reasonable to propose that there may be cooperation between different mitophagy pathways in mammalian cells exposed to hypoxia. However, the expression of BNIP3 and NIX is induced by HIF-1α in response to hypoxia [87,88], little is known about the transcriptional regulation of FUNDC1 during hypoxia [15].

5. Perspectives

In eukaryocytes, mitophagy has evolved to regulate both mitochondrial quality and quantity. Thus, it is not surprising that there are common features of mitophagy that are shared between yeast and mammals. Indeed, the function and the regulation of FUNDC1 strongly resemble those of Atg32. There may be other mitophagy receptors yet to be identified in mammalian cells that have evolved to respond to various (patho)physiological circumstances.

Mitophagy may be responsible for different aspects of mitochondrial clearance: 1) the basal level of mitochondrial turnover; 2) the complete elimination of mitochondria during red blood cell maturation; and 3) the removal of damaged mitochondria in response to the acute mitochondrial damage or energy crisis. As described above, several distinct mechanisms have been described to be involved in mitochondrial quality control. It appears that distinct mitophagy mechanisms are activated in response to different mitochondrial stresses. For example, NIX is required for mitochondrial elimination during red blood cell maturation; the PINK1/Parkin pathway has been suggested to be important to mitophagy in response to acute mitochondrial stresses such as high-dose FCCP; FUNDC1 was found to mediate mitophagy in response to hypoxia and FCCP treatment. Alternatively, there is evidence suggesting that different pathways may cooperate or share regulatory molecules. NIX has been found to participate in the translocation of Parkin and to be essential for the CCCP-induced depolarization of mitochondria during the early stage of CCCP treatment in a BH3-domain-dependent manner [89], suggesting that NIX may act upstream of Parkin to mediate mitophagy. In addition, it has been reported that PGAM5 may negatively regulate the PINK1 pathway-related maintenance of mitochondria in Drosophila [90]. Another recent study showed that PGAM5-deficient mice exhibit a parkinsonian movement phenotype and that PGAM5 is required for the stabilization of PINK1 on damaged mitochondria [91].

Table 1
Atg32 and FUNDC1: common points and differences.

		Atg32	FUNDC1
Location		Outer mitochondrial membrane	Outer mitochondrial membrane
AIM/LIR motif		WQAI	YEVL
Post-translational regulation	Upstream Kinases	Atg1: unclear role	ULK1: phosphorylation of Ser17 of FUNDC1 to enhance interaction between FUDNC1 and LC3 during mitophagy
		CK2: phosphorylation of Ser114 and Ser119 of Atg32 to enhance the Atg-32–Atg11 interaction during mitophagy Hog1 and Slt2: unclear role	CK2: phosphorylation of Ser13 of FUNDC1 to prevent mitophagy under normal conditions Src: phosphorylation of Tyr18 of FUNDC1 to prevent mitophagy under normal conditions
	Upstream phosphatase	Unknown	PGAM5: dephosphorylation of Ser13 of FUNDC1 to promote mitophagy under normal conditions
Function model		Recruitment of the isolation membrane to mitochondria through Atg32–Atg8 interaction and Atg32–Atg11–Atg8 interaction	Recruitment of the isolation membrane to mitochondria through FUNDC1–LC3 interaction
Regulation of expression level		Temporally upregulation prior to mitophagy under respiratory conditions, and subsequently degraded in autophagy-dependent and autophagy-independent manner during mitophagy	MicroRNA-137 suppresses the expression of FUNDC1 under normal conditions; Degradation during mitophagy in response to hypoxia; Degradation manner remains unknown

We also demonstrated that PGAM5 plays an essential role in FUNDC1-mediated mitophagy via the dephosphorylation of FUNDC1 at Ser13 in HeLa cells [78]. In addition to mitophagy receptors or adaptor proteins on mitochondria, the redistribution of cardiolipin is another novel potential mitophagy signal in neuronal cells [92]. In response to pro-mitophagy stimuli, cardiolipin externalizes to the outer mitochondrial membrane and then recruits mitochondria targeted for degradation to the isolation membrane via its association with LC3, which may act downstream of PINK1 or Parkin [92]. These findings suggest that distinct mitophagy pathways cooperate to regulate mitochondrial homeostasis. However, most of the current studies of mitophagy have been performed using cultured cells. Thus, it is important to develop an appropriate animal model to address how these distinct mechanisms cooperate in mitochondrial quality and quantity control under physiologic conditions.

Conflict of interest statements

The authors declare no conflict of interest.

Acknowledgments

This work was supported by the 973 program project of the Ministry of Science and Technology (China) (No. 2011CB910903 and 2013CB531200) and by grants from the National Natural Science Foundation of China (31123004 and 31471306).

References

[1] D.J. Klionsky, Autophagy: from phenomenology to molecular understanding in less than a decade, Nat. Rev. Mol. Cell Biol. 8 (2007) 931–937.
[2] C. De Duve, R. Wattiaux, Functions of lysosomes, Annu. Rev. Physiol. 28 (1966) 435–492.
[3] D.J. Klionsky, S.D. Emr, Autophagy as a regulated pathway of cellular degradation, Science 290 (2000) 1717–1721.
[4] C. Kraft, M. Peter, K. Hofmann, Selective autophagy: ubiquitin-mediated recognition and beyond, Nat. Cell Biol. 12 (2010) 836–841.
[5] I. Kim, S. Rodriguez-Enriquez, J.J. Lemasters, Selective degradation of mitochondria by mitophagy, Arch. Biochem. Biophys. 462 (2007) 245–253.
[6] H.U. Simon, A. Haj-Yehia, F. Levi-Schaffer, Role of reactive oxygen species (ROS) in apoptosis induction, Apoptosis 5 (2000) 415–418.
[7] F.M. Yakes, B. Van Houten, Mitochondrial DNA damage is more extensive and persists longer than nuclear DNA damage in human cells following oxidative stress, Proc. Natl. Acad. Sci. U. S. A. 94 (1997) 514–519.
[8] Y. Kurihara, T. Kanki, Y. Aoki, Y. Hirota, T. Saigusa, T. Uchiumi, D. Kang, Mitophagy plays an essential role in reducing mitochondrial production of reactive oxygen species and mutation of mitochondrial DNA by maintaining mitochondrial quantity and quality in yeast, J. Biol. Chem. 287 (2012) 3265–3272.
[9] C.H. Damsky, Environmentally induced changes in mitochondria and endoplasmic reticulum of *Saccharomyces carlsbergensis* yeast, J. Cell Biol. 71 (1976) 123–135.
[10] J.J. Lemasters, Selective mitochondrial autophagy, or mitophagy, as a targeted defense against oxidative stress, mitochondrial dysfunction, and aging, Rejuvenation Res. 8 (2005) 3–5.
[11] R. Scherz-Shouval, Z. Elazar, ROS, mitochondria and the regulation of autophagy, Trends Cell Biol. 17 (2007) 422–427.
[12] T. Kanki, K. Wang, Y. Cao, M. Baba, D.J. Klionsky, Atg32 is a mitochondrial protein that confers selectivity during mitophagy, Dev. Cell 17 (2009) 98–109.
[13] K. Okamoto, N. Kondo-Okamoto, Y. Ohsumi, Mitochondria-anchored receptor Atg32 mediates degradation of mitochondria via selective autophagy, Dev. Cell 17 (2009) 87–97.
[14] I. Novak, V. Kirkin, D.G. McEwan, J. Zhang, P. Wild, A. Rozenknop, V. Rogov, F. Lohr, D. Popovic, A. Occhipinti, A.S. Reichert, J. Terzic, V. Dotsch, P.A. Ney, I. Dikic, Nix is a selective autophagy receptor for mitochondrial clearance, EMBO Rep. 11 (2010) 45–51.
[15] L. Liu, D. Feng, G. Chen, M. Chen, Q. Zheng, P. Song, Q. Ma, C. Zhu, R. Wang, W. Qi, L. Huang, P. Xue, B. Li, X. Wang, H. Jin, J. Wang, F. Yang, P. Liu, Y. Zhu, S. Sui, Q. Chen, Mitochondrial outer-membrane protein FUNDC1 mediates hypoxia-induced mitophagy in mammalian cells, Nat. Cell Biol. 14 (2012) 177–185.
[16] D. Narendra, J.E. Walker, R. Youle, Mitochondrial quality control mediated by PINK1 and Parkin: links to Parkinsonism, Cold Spring Harb. Perspect. Biol. 4 (2012).
[17] I. Kissova, M. Deffieu, S. Manon, N. Camougrand, Uth1p is involved in the autophagic degradation of mitochondria, J. Biol. Chem. 279 (2004) 39068–39074.
[18] R. Tal, G. Winter, N. Ecker, D.J. Klionsky, H. Abeliovich, Aup1p, a yeast mitochondrial protein phosphatase homolog, is required for efficient stationary phase mitophagy and cell survival, J. Biol. Chem. 282 (2007) 5617–5624.
[19] M. Priault, B. Salin, J. Schaeffer, F.M. Vallette, J.P. di Rago, J.C. Martinou, Impairing the bioenergetic status and the biogenesis of mitochondria triggers mitophagy in yeast, Cell Death Differ. 12 (2005) 1613–1621.
[20] K. Nowikovsky, S. Reipert, R.J. Devenish, R.J. Schweyen, Mdm38 protein depletion causes loss of mitochondrial K^+/H^+ exchange activity, osmotic swelling and mitophagy, Cell Death Differ. 14 (2007) 1647–1656.
[21] Y. Zhang, H. Qi, R. Taylor, W. Xu, L.F. Liu, S. Jin, The role of autophagy in mitochondria maintenance: characterization of mitochondrial functions in autophagy-deficient *S. cerevisiae* strains, Autophagy 3 (2007) 337–346.
[22] N. Kondo-Okamoto, N.N. Noda, S.W. Suzuki, H. Nakatogawa, I. Takahashi, M. Matsunami, A. Hashimoto, F. Inagaki, Y. Ohsumi, K. Okamoto, Autophagy-related protein 32 acts as autophagic degron and directly initiates mitophagy, J. Biol. Chem. 287 (2012) 10631–10638.
[23] K. Wang, M. Jin, X. Liu, D.J. Klionsky, Proteolytic processing of Atg32 by the mitochondrial i-AAA protease Yme1 regulates mitophagy, Autophagy 9 (2013) 1828–1836.
[24] E. Welter, M. Montino, R. Reinhold, P. Schlotterhose, R. Krick, J. Dudek, P. Rehling, M. Thumm, Uth1 is a mitochondrial inner membrane protein dispensable for post-log-phase and rapamycin-induced mitophagy, FEBS J. 280 (2013) 4970–4982.
[25] T. Kanki, K. Wang, D.J. Klionsky, A genomic screen for yeast mutants defective in mitophagy, Autophagy 6 (2010) 278–280.
[26] T. Kanki, K. Wang, M. Baba, C.R. Bartholomew, M.A. Lynch-Day, Z. Du, J. Geng, K. Mao, Z. Yang, W.L. Yen, D.J. Klionsky, A genomic screen for yeast mutants defective in selective mitochondria autophagy, Mol. Biol. Cell 20 (2009) 4730–4738.
[27] Y. Aoki, T. Kanki, Y. Hirota, Y. Kurihara, T. Saigusa, T. Uchiumi, D. Kang, Phosphorylation of Serine 114 on Atg32 mediates mitophagy, Mol. Biol. Cell 22 (2011) 3206–3217.
[28] T. Kanki, D.J. Klionsky, Mitophagy in yeast occurs through a selective mechanism, J. Biol. Chem. 283 (2008) 32386–32393.
[29] M. Deffieu, I. Bhatia-Kissova, B. Salin, A. Galinier, S. Manon, N. Camougrand, Glutathione participates in the regulation of mitophagy in yeast, J. Biol. Chem. 284 (2009) 14828–14837.
[30] T. Kanki, Y. Kurihara, X. Jin, T. Goda, Y. Ono, M. Aihara, Y. Hirota, T. Saigusa, Y. Aoki, T. Uchiumi, D. Kang, Casein kinase 2 is essential for mitophagy, EMBO Rep. 14 (2013) 788–794.
[31] K. Mao, K. Wang, M. Zhao, T. Xu, D.J. Klionsky, Two MAPK-signaling pathways are required for mitophagy in *Saccharomyces cerevisiae*, J. Cell Biol. 193 (2011) 755–767.
[32] T. Kitada, S. Asakawa, N. Hattori, H. Matsumine, Y. Yamamura, S. Minoshima, M. Yokochi, Y. Mizuno, N. Shimizu, Mutations in the parkin gene cause autosomal recessive juvenile parkinsonism, Nature 392 (1998) 605–608.
[33] C.B. Lucking, A. Durr, V. Bonifati, J. Vaughan, G. De Michele, T. Gasser, B.S. Harhangi, G. Meco, P. Denefle, N.W. Wood, Y. Agid, A. Brice, Association between early-onset Parkinson's disease and mutations in the parkin gene, N. Engl. J. Med. 342 (2000) 1560–1567.
[34] E.M. Valente, P.M. Abou-Sleiman, V. Caputo, M.M. Muqit, K. Harvey, S. Gispert, Z. Ali, D. Del Turco, A.R. Bentivoglio, D.G. Healy, A. Albanese, R. Nussbaum, R. Gonzalez-Maldonado, T. Deller, S. Salvi, P. Cortelli, W.P. Gilks, D.S. Latchman, R.J. Harvey, B. Dallapiccola, G. Auburger, N.W. Wood, Hereditary early-onset Parkinson's disease caused by mutations in PINK1, Science 304 (2004) 1158–1160.
[35] H. Shimura, N. Hattori, S. Kubo, Y. Mizuno, S. Asakawa, S. Minoshima, N. Shimizu, K. Iwai, T. Chiba, K. Tanaka, T. Suzuki, Familial Parkinson disease gene product, parkin, is a ubiquitin-protein ligase, Nat. Genet. 25 (2000) 302–305.
[36] Y. Zhang, J. Gao, K.K. Chung, H. Huang, V.L. Dawson, T.M. Dawson, Parkin functions as an E2-dependent ubiquitin-protein ligase and promotes the degradation of the synaptic vesicle-associated protein, CDCrel-1, Proc. Natl. Acad. Sci. U. S. A. 97 (2000) 13354–13359.
[37] I.E. Clark, M.W. Dodson, C. Jiang, J.H. Cao, J.R. Huh, J.H. Seol, S.J. Yoo, B.A. Hay, M. Guo, Drosophila pink1 is required for mitochondrial function and interacts genetically with parkin, Nature 441 (2006) 1162–1166.
[38] J. Park, S.B. Lee, S. Lee, Y. Kim, S. Song, S. Kim, E. Bae, J. Kim, M. Shong, J.M. Kim, J. Chung, Mitochondrial dysfunction in Drosophila PINK1 mutants is complemented by parkin, Nature 441 (2006) 1157–1161.
[39] Y. Yang, S. Gehrke, Y. Imai, Z. Huang, Y. Ouyang, J.W. Wang, L. Yang, M.F. Beal, H. Vogel, B. Lu, Mitochondrial pathology and muscle and dopaminergic neuron degeneration caused by inactivation of Drosophila Pink1 is rescued by Parkin, Proc. Natl. Acad. Sci. U. S. A. 103 (2006) 10793–10798.
[40] A.W. Greene, K. Grenier, M.A. Aguileta, S. Muise, R. Farazifard, M.E. Haque, H.M. McBride, D.S. Park, E.A. Fon, Mitochondrial processing peptidase regulates PINK1 processing, import and Parkin recruitment, EMBO Rep. 13 (2012) 378–385.
[41] S.M. Jin, M. Lazarou, C. Wang, L.A. Kane, D.P. Narendra, R.J. Youle, Mitochondrial membrane potential regulates PINK1 import and proteolytic destabilization by PARL, J. Cell Biol. 191 (2010) 933–942.
[42] N. Matsuda, S. Sato, K. Shiba, K. Okatsu, K. Saisho, C.A. Gautier, Y.S. Sou, S. Saiki, S. Kawajiri, F. Sato, M. Kimura, M. Komatsu, N. Hattori, K. Tanaka, PINK1 stabilized by mitochondrial depolarization recruits Parkin to damaged mitochondria and activates latent Parkin for mitophagy, J. Cell Biol. 189 (2010) 211–221.
[43] D.P. Narendra, S.M. Jin, A. Tanaka, D.F. Suen, C.A. Gautier, J. Shen, M.R. Cookson, R.J. Youle, PINK1 is selectively stabilized on impaired mitochondria to activate Parkin, PLoS Biol. 8 (2010) e1000298.
[44] C. Vives-Bauza, C. Zhou, Y. Huang, M. Cui, R.L. de Vries, J. Kim, J. May, M.A. Tocilescu, W. Liu, H.S. Ko, J. Magrane, D.J. Moore, V.L. Dawson, R. Grailhe, T.M. Dawson, C. Li, K. Tieu, S. Przedborski, PINK1-dependent recruitment of Parkin to mitochondria in mitophagy, Proc. Natl. Acad. Sci. U. S. A. 107 (2010) 378–383.
[45] C. Kondapalli, A. Kazlauskaite, N. Zhang, H.I. Woodroof, D.G. Campbell, R. Gourlay, L. Burchell, H. Walden, T.J. Macartney, M. Deak, A. Knebel, D.R. Alessi, M.M. Muqit, PINK1 is activated by mitochondrial membrane potential depolarization and stimulates Parkin E3 ligase activity by phosphorylating Serine 65, FEBS Open Bio 2 (2012) 120080.

[46] L.A. Kane, M. Lazarou, A.I. Fogel, Y. Li, K. Yamano, S.A. Sarraf, S. Banerjee, R.J. Youle, PINK1 phosphorylates ubiquitin to activate Parkin E3 ubiquitin ligase activity, J. Cell Biol. 205 (2014) 143–153.
[47] A. Kazlauskaite, C. Kondapalli, R. Gourlay, D.G. Campbell, M.S. Ritorto, K. Hofmann, D.R. Alessi, A. Knebel, M. Trost, M.M. Muqit, Parkin is activated by PINK1-dependent phosphorylation of ubiquitin at Ser65, Biochem. J. 460 (2014) 127–139.
[48] F. Koyano, K. Okatsu, H. Kosako, Y. Tamura, E. Go, M. Kimura, Y. Kimura, H. Tsuchiya, H. Yoshihara, T. Hirokawa, T. Endo, E.A. Fon, J.F. Trempe, Y. Saeki, K. Tanaka, N. Matsuda, Ubiquitin is phosphorylated by PINK1 to activate parkin, Nature 510 (2014) 162–166.
[49] A. Tanaka, M.M. Cleland, S. Xu, D.P. Narendra, D.F. Suen, M. Karbowski, R.J. Youle, Proteasome and p97 mediate mitophagy and degradation of mitofusins induced by Parkin, J. Cell Biol. 191 (2010) 1367–1380.
[50] S. Liu, T. Sawada, S. Lee, W. Yu, G. Silverio, P. Alapatt, I. Millan, A. Shen, W. Saxton, T. Kanao, R. Takahashi, N. Hattori, Y. Imai, B. Lu, Parkinson's disease-associated kinase PINK1 regulates Miro protein level and axonal transport of mitochondria, PLoS Genet. 8 (2012) e1002537.
[51] H. Wang, P. Song, L. Du, W. Tian, W. Yue, M. Liu, D. Li, B. Wang, Y. Zhu, C. Cao, J. Zhou, Q. Chen, Parkin ubiquitinates Drp1 for proteasome-dependent degradation: implication of dysregulated mitochondrial dynamics in Parkinson disease, J. Biol. Chem. 286 (2011) 11649–11658.
[52] J.H. Shin, H.S. Ko, H. Kang, Y. Lee, Y.I. Lee, O. Pletinkova, J.C. Troconso, V.L. Dawson, T.M. Dawson, PARIS (ZNF746) repression of PGC-1alpha contributes to neurodegeneration in Parkinson's disease, Cell 144 (2011) 689–702.
[53] K. Okatsu, K. Saisho, M. Shimanuki, K. Nakada, H. Shitara, Y.S. Sou, M. Kimura, S. Sato, N. Hattori, M. Komatsu, K. Tanaka, N. Matsuda, p62/SQSTM1 cooperates with Parkin for perinuclear clustering of depolarized mitochondria, Genes Cells 15 (2010) 887–900.
[54] D. Narendra, L.A. Kane, D.N. Hauser, I.M. Fearnley, R.J. Youle, p62/SQSTM1 is required for Parkin-induced mitochondrial clustering but not mitophagy; VDAC1 is dispensable for both, Autophagy 6 (2010) 1090–1106.
[55] S. Geisler, K.M. Holmstrom, D. Skujat, F.C. Fiesel, O.C. Rothfuss, P.J. Kahle, W. Springer, PINK1/Parkin-mediated mitophagy is dependent on VDAC1 and p62/SQSTM1, Nat. Cell Biol. 12 (2010) 119–131.
[56] Y. Chen, G.W. Dorn II, PINK1-phosphorylated mitofusin 2 is a Parkin receptor for culling damaged mitochondria, Science 340 (2013) 471–475.
[57] Y.C. Wong, E.L. Holzbaur, Optineurin is an autophagy receptor for damaged mitochondria in parkin-mediated mitophagy that is disrupted by an ALS-linked mutation, Proc. Natl. Acad. Sci. U. S. A. 111 (2014) E4439–E4448.
[58] S. Rikka, M.N. Quinsay, R.L. Thomas, D.A. Kubli, X. Zhang, A.N. Murphy, A.B. Gustafsson, Bnip3 impairs mitochondrial bioenergetics and stimulates mitochondrial turnover, Cell Death Differ. 18 (2011) 721–731.
[59] R.L. Schweers, J. Zhang, M.S. Randall, M.R. Loyd, W. Li, F.C. Dorsey, M. Kundu, J.T. Opferman, J.L. Cleveland, J.L. Miller, P.A. Ney, NIX is required for programmed mitochondrial clearance during reticulocyte maturation, Proc. Natl. Acad. Sci. U. S. A. 104 (2007) 19500–19505.
[60] M. Schwarten, J. Mohrluder, P. Ma, M. Stoldt, Y. Thielmann, T. Stangler, N. Hersch, B. Hoffmann, R. Merkel, D. Willbold, Nix directly binds to GABARAP: a possible crosstalk between apoptosis and autophagy, Autophagy 5 (2009) 690–698.
[61] H. Sandoval, P. Thiagarajan, S.K. Dasgupta, A. Schumacher, J.T. Prchal, M. Chen, J. Wang, Essential role for Nix in autophagic maturation of erythroid cells, Nature 454 (2008) 232–235.
[62] A. Diwan, A.G. Koesters, A.M. Odley, S. Pushkaran, C.P. Baines, B.T. Spike, D. Daria, A.G. Jegga, H. Geiger, B.J. Aronow, J.D. Molkentin, K.F. Macleod, T.A. Kalfa, G.W. Dorn II, Unrestrained erythroblast development in Nix−/− mice reveals a mechanism for apoptotic modulation of erythropoiesis, Proc. Natl. Acad. Sci. U. S. A. 104 (2007) 6794–6799.
[63] M. Kundu, T. Lindsten, C.Y. Yang, J. Wu, F. Zhao, J. Zhang, M.A. Selak, P.A. Ney, C.B. Thompson, Ulk1 plays a critical role in the autophagic clearance of mitochondria and ribosomes during reticulocyte maturation, Blood 112 (2008) 1493–1502.
[64] M. Mortensen, D.J. Ferguson, M. Edelmann, B. Kessler, K.J. Morten, M. Komatsu, A.K. Simon, Loss of autophagy in erythroid cells leads to defective removal of mitochondria and severe anemia in vivo, Proc. Natl. Acad. Sci. U. S. A. 107 (2010) 832–837.
[65] S. Honda, S. Arakawa, Y. Nishida, H. Yamaguchi, E. Ishii, S. Shimizu, Ulk1-mediated Atg5-independent macroautophagy mediates elimination of mitochondria from embryonic reticulocytes, Nat. Commun. 5 (2014) 4004.
[66] Y. Nishida, S. Arakawa, K. Fujitani, H. Yamaguchi, T. Mizuta, T. Kanaseki, M. Komatsu, K. Otsu, Y. Tsujimoto, S. Shimizu, Discovery of Atg5/Atg7-independent alternative macroautophagy, Nature 461 (2009) 654–658.
[67] C. Grullich, R.M. Duvoisin, M. Wiedmann, K. van Leyen, Inhibition of 15-lipoxygenase leads to delayed organelle degradation in the reticulocyte, FEBS Lett. 489 (2001) 51–54.
[68] W. Aerbajinai, M. Giattina, Y.T. Lee, M. Raffeld, J.L. Miller, The proapoptotic factor Nix is coexpressed with Bcl-xL during terminal erythroid differentiation, Blood 102 (2003) 712–717.
[69] C. Mammucari, G. Milan, V. Romanello, E. Masiero, R. Rudolf, P. Del Piccolo, S.J. Burden, R. Di Lisi, C. Sandri, J. Zhao, A.L. Goldberg, S. Schiaffino, M. Sandri, FoxO3 controls autophagy in skeletal muscle in vivo, Cell Metab. 6 (2007) 458–471.
[70] W. Li, X. Zhang, H. Zhuang, H.G. Chen, Y. Chen, W. Tian, W. Wu, Y. Li, S. Wang, L. Zhang, L. Li, B. Zhao, S. Sui, Z. Hu, D. Feng, MicroRNA-137 is a novel hypoxia-responsive microRNA that inhibits mitophagy via regulation of two mitophagy receptors FUNDC1 and NIX, J. Biol. Chem. 289 (2014) 10691–10701.
[71] Y. Zhu, S. Massen, M. Terenzio, V. Lang, S. Chen-Lindner, R. Eils, I. Novak, I. Dikic, A. Hamacher-Brady, N.R. Brady, Modulation of serines 17 and 24 in the LC3-interacting region of Bnip3 determines pro-survival mitophagy versus apoptosis, J. Biol. Chem. 288 (2013) 1099–1113.
[72] H. Nakatogawa, Y. Ichimura, Y. Ohsumi, Atg8, a ubiquitin-like protein required for autophagosome formation, mediates membrane tethering and hemifusion, Cell 130 (2007) 165–178.
[73] Y. Ichimura, T. Kumanomidou, Y.S. Sou, T. Mizushima, J. Ezaki, T. Ueno, E. Kominami, T. Yamane, K. Tanaka, M. Komatsu, Structural basis for sorting mechanism of p62 in selective autophagy, J. Biol. Chem. 283 (2008) 22847–22857.
[74] S. Pankiv, T.H. Clausen, T. Lamark, A. Brech, J.A. Bruun, H. Outzen, A. Overvatn, G. Bjorkoy, T. Johansen, p62/SQSTM1 binds directly to Atg8/LC3 to facilitate degradation of ubiquitinated protein aggregates by autophagy, J. Biol. Chem. 282 (2007) 24131–24145.
[75] V. Kirkin, T. Lamark, Y.S. Sou, G. Bjorkoy, J.L. Nunn, J.A. Bruun, E. Shvets, D.G. McEwan, T.H. Clausen, P. Wild, I. Bilusic, J.P. Theurillat, A. Overvatn, T. Ishii, Z. Elazar, M. Komatsu, I. Dikic, T. Johansen, A role for NBR1 in autophagosomal degradation of ubiquitinated substrates, Mol. Cell 33 (2009) 505–516.
[76] P. Wild, H. Farhan, D.G. McEwan, S. Wagner, V.V. Rogov, N.R. Brady, B. Richter, J. Korac, O. Waidmann, C. Choudhary, V. Dotsch, D. Bumann, I. Dikic, Phosphorylation of the autophagy receptor optineurin restricts Salmonella growth, Science 333 (2011) 228–233.
[77] T. Johansen, T. Lamark, Selective autophagy mediated by autophagic adapter proteins, Autophagy 7 (2011) 279–296.
[78] G. Chen, Z. Han, D. Feng, Y. Chen, L. Chen, H. Wu, L. Huang, C. Zhou, X. Cai, C. Fu, L. Duan, X. Wang, L. Liu, X. Liu, Y. Shen, Y. Zhu, Q. Chen, A regulatory signaling loop comprising the PGAM5 phosphatase and CK2 controls receptor-mediated mitophagy, Mol. Cell 54 (2014) 362–377.
[79] H. Wu, D. Xue, G. Chen, Z. Han, L. Huang, C. Zhu, X. Wang, H. Jin, J. Wang, Y. Zhu, L. Liu, Q. Chen, The BCL2L1 and PGAM5 axis defines hypoxia-induced receptor-mediated mitophagy, Autophagy 10 (2014) 1712–1725.
[80] M.C. Maiuri, G. Le Toumelin, A. Criollo, J.C. Rain, F. Gautier, P. Juin, E. Tasdemir, G. Pierron, K. Troulinaki, N. Tavernarakis, J.A. Hickman, O. Geneste, G. Kroemer, Functional and physical interaction between Bcl-X(L) and a BH3-like domain in Beclin-1, EMBO J. 26 (2007) 2527–2539.
[81] W. Wu, W. Tian, Z. Hu, G. Chen, L. Huang, W. Li, X. Zhang, P. Xue, C. Zhou, L. Liu, Y. Zhu, L. Li, L. Zhang, S. Sui, B. Zhao, D. Feng, ULK1 translocates to mitochondria and phosphorylates FUNDC1 to regulate mitophagy, EMBO Rep. 15 (2014) 566–575.
[82] M. Hockel, P. Vaupel, Tumor hypoxia: definitions and current clinical, biologic, and molecular aspects, J. Natl. Cancer Inst. 93 (2001) 266–276.
[83] P.H. Maxwell, G.U. Dachs, J.M. Gleadle, L.G. Nicholls, A.L. Harris, I.J. Stratford, O. Hankinson, C.W. Pugh, P.J. Ratcliffe, Hypoxia-inducible factor-1 modulates gene expression in solid tumors and influences both angiogenesis and tumor growth, Proc. Natl. Acad. Sci. U. S. A. 94 (1997) 8104–8109.
[84] A.L. Harris, Hypoxia—a key regulatory factor in tumour growth, Nat. Rev. Cancer 2 (2002) 38–47.
[85] H. Wu, Q. Chen, Hypoxia activation of mitophagy and its role in disease pathogenesis, Antioxid. Redox Signal. 22 (2015) 1032–1046.
[86] H. Zhang, M. Bosch-Marce, L.A. Shimoda, Y.S. Tan, J.H. Baek, J.B. Wesley, F.J. Gonzalez, G.L. Semenza, Mitochondrial autophagy is an HIF-1-dependent adaptive metabolic response to hypoxia, J. Biol. Chem. 283 (2008) 10892–10903.
[87] A. Vengellur, J.J. LaPres, The role of hypoxia inducible factor 1alpha in cobalt chloride induced cell death in mouse embryonic fibroblasts, Toxicol. Sci. 82 (2004) 638–646.
[88] M.G. Yussman, T. Toyokawa, A. Odley, R.A. Lynch, G. Wu, M.C. Colbert, B.J. Aronow, J.N. Lorenz, G.W. Dorn II, Mitochondrial death protein Nix is induced in cardiac hypertrophy and triggers apoptotic cardiomyopathy, Nat. Med. 8 (2002) 725–730.
[89] W.X. Ding, H.M. Ni, M. Li, Y. Liao, X. Chen, D.B. Stolz, G.W. Dorn II, X.M. Yin, Nix is critical to two distinct phases of mitophagy, reactive oxygen species-mediated autophagy induction and Parkin-ubiquitin-p62-mediated mitochondrial priming, J. Biol. Chem. 285 (2010) 27879–27890.
[90] Y. Imai, T. Kanao, T. Sawada, Y. Kobayashi, Y. Moriwaki, Y. Ishida, K. Takeda, H. Ichijo, B. Lu, R. Takahashi, The loss of PGAM5 suppresses the mitochondrial degeneration caused by inactivation of PINK1 in Drosophila, PLoS Genet. 6 (2010) e1001229.
[91] W. Lu, S.S. Karuppagounder, D.A. Springer, M.D. Allen, L. Zheng, B. Chao, Y. Zhang, V.L. Dawson, T.M. Dawson, M. Lenardo, Genetic deficiency of the mitochondrial protein PGAM5 causes a Parkinson's-like movement disorder, Nat. Commun. 5 (2014) 4930.
[92] C.T. Chu, J. Ji, R.K. Dagda, J.F. Jiang, Y.Y. Tyurina, A.A. Kapralov, V.A. Tyurin, N. Yanamala, I.H. Shrivastava, D. Mohammadyani, K.Z. Qiang Wang, J. Zhu, J. Klein-Seetharaman, K. Balasubramanian, A.A. Amoscato, G. Borisenko, Z. Huang, A.M. Gusdon, A. Cheikhi, E.K. Steer, R. Wang, C. Baty, S. Watkins, I. Bahar, H. Bayir, V.E. Kagan, Cardiolipin externalization to the outer mitochondrial membrane acts as an elimination signal for mitophagy in neuronal cells, Nat. Cell Biol. 15 (2013) 1197–1205.