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Mitophagy mechanisms and role in human diseases

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Abstract

Mitophagy is a process of mitochondrial turnover through lysosomal mediated autophagy activities. This review will highlight recent studies that have identified mediators of mitophagy in response to starvation, loss of mitochondrial membrane potential or perturbation of mitochondrial integrity. Furthermore, we will review evidence of mitophagy dysfunction in various human diseases and discuss the potential for therapeutic interventions that target mitophagy processes.

1. Introduction

Mitochondria are important for cell metabolism and ATP generation via oxidative phosphorylation through the electron transport chain, fatty acid oxidation, and TCA cycle. In addition, mitochondria are responsible for their own DNA replication, transcription and translation of mitochondrial proteins, import of nuclear-encoded proteins, calcium storage, production and scavenging of oxidants, signaling, and sequestration of pro-apoptotic proteins to sustain cell survival (Newmeyer and Ferguson-Miller, 2003; Mitchell et al., 2013a; Dodson et al., 2013). Maintenance of a healthy mitochondrial population is essential for cellular function and survival, and is controlled by balancing biogenesis and turnover of mitochondria via autophagy (mitophagy) (Lee et al., 2012;Dodson et al., 2013;Zhang, 2013;Hill et al., 2012) This review will focus on the mechanisms by which mitochondria are removed by mitophagy, and highlight evidence that mitophagy dysregulation contributes to human diseases.

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2. Molecular mechanisms of mitochondrial quality control through mitophagy

2.1 Mitophagy mediated by adaptor proteins

Autophagy is a lysosomal mediated degradation program (Lee et al., 2012;Dodson et al., 2013;Zhang 2013;Hill et al., 2012). The term “mitophagy” was officially proposed by JJ Lemasters in 2005 to describe a selective process of mitochondrial degradation by autophagy (Lemasters, 2005). Since then the molecular mechanisms of selective mitophagy have been described in some detail, particularly in yeast. The mitochondrial outer membrane protein Uth1p was the first protein identified to be essential for autophagic removal of mitochondria in yeast in response to rapamycin or nitrogen starvation, while dispensable for non-specific autophagy activities (Kissova et al., 2004). Another example is Aup1p, which is located in the mitochondrial intermembrane space and is important for mitophagy during growth in stationary phase (Tal et al., 2007). It has been shown that Atg11 is dispensable for non-specific autophagy but essential for selective autophagy. Atg32 localizes to the outer mitochondrial membrane in response to starvation or when cells reach the post-log phase in non-fermentable glycerol medium (Kanki et al., 2009;Okamoto et al., 2009). An increase in Atg32 levels occurs in post-log phase, and is mitigated by N-acetylcysteine, suggesting regulation of Atg32 levels by intracellular glutathione (Okamoto et al., 2009). Atg32 also interacts with Atg8 and Atg11, thus recruiting mitochondria to the autophagosome (Kanki et al., 2009;Okamoto et al., 2009). The C-terminus on Atg11 interacts with the N-terminus on Atg32 when Atg32 is phosphorylated at Ser-114 and 119 by casein kinase 2, and it has been shown that the phosphorylation is also dependent on Pbs1-Hog1 activities (Aoki et al., 2011;Kanki et al., 2013). Proteolytic cleavage of the C-terminus of Atg32 by mitochondrial i-AAA protease Yme1 also enhances the interaction between Atg32 and Atg11 (Wang et al., 2013). These findings demonstrate critical protein-protein interactions in yeast that allows for specific, regulated removal of mitochondria using the autophagic machinery (Fig.1).

Less is known about selective adaptor proteins in mammalian cells, and there is currently no known mammalian homolog of Uth1 or Atg32. It has been observed that during mammalian erythrocyte maturation, NIX targets to the mitochondria, binds LC3 or LC3 homologs, and plays an important role in mitophagy (Sandoval et al., 2008;Novak et al., 2010). Additionally, BNIP3 and FUNDC1 also contain LC3 interacting regions and play a role in mitophagy under hypoxic conditions (Zhang et al., 2008;Liu et al., 2012). In cells undergoing high rates of oxidative phosphorylation, the GTPase RHEB can be recruited to the mitochondria, where it interacts with NIX and LC3 to promote mitophagy and maintain an active and healthy mitochondrial pool (Melser et al., 2013).

2.2 Mitophagy regulation by mitochondrial dynamics and membrane potential

Mitochondrial dynamics are emerging as an important aspect of cellular physiology, and play an important role in regulating mitophagy (Twig and Shirihai, 2011). In yeast, the Atg32/Atg11 complex recruits the fission machinery in response to nitrogen starvation through an interaction between Atg11 and Dnm1 (Fig.1). Mutations of the Atg11-interaction domain on Dnm1 protein decreased mitophagy (Mao et al., 2013). In mammalian cells, mitophagy has been shown to occur coordinately with fission events in hepatocytes (Kim

and Lemasters, 2011). Inhibition of mitochondrial fission by either *Fis1* siRNA or a dominant negative form of DRP-1 prevents mitophagy in INS-1 β-cells (Twig G et al., 2008). In mouse embryonic fibroblasts (MEFs), elimination of either glutamine or amino acids from the growth medium, but not elimination of glucose or serum, resulted in mitochondrial tubulation. MEFs with *Opa1* or *Mfn2* gene knockout exhibited increased mitophagy during starvation (Rambold et al., 2011). The mechanisms through which changes of fission or fusion due to *Drp1*, *Opa1* or *Mfn2* knockdown or knockout impact mitophagy may involve changes not only in mitochondrial morphology but also in mitochondrial membrane potential and bioenergetics (Frank et al., 2001;Olichon et al., 2003;Duvezin-Caubet et al., 2006;Narendra et al., 2008). Recent evidence also suggests that FIS1 may act downstream of DRP-1, in response to calcium ionophores in *C.elegans*, or to Antimycin A or CCCP in HCT116 cells, to initiate formation of nascent mitophagosomes by participation in the mitochondrion-associated membrane (MAM) complex (Shen et al., 2014). These studies demonstrate that mitochondrial fission/fusion machinery plays a pivotal role in the regulation of mitophagy.

In addition to fission and fusion, mitochondrial membrane potential plays an important role in mitophagy. In rat hepatocytes, serum deprivation has been shown to induce mitochondrial depolarization and engulfment by autophagosomes (Elmore et al., 2001). How mitochondrial depolarization leads to mitophagy has been extensively studied in the context of understanding potential pathogenic mechanisms of Parkinson's disease, and it has been found that recessive genes identified in familial Parkinson's disease, *PARKIN*, *PINK1* and *DJ-1*, encode proteins involved in mitophagy. Studies using *Drosophila* models and established human cell lines have found that upon depolarization, PINK1 (PTEN–induced putative kinase 1) is imported into the mitochondria by the Translocase of the Outer Membrane (TOM) and Translocase of the Inner Membrane (TIM) complexes. PINK1 then anchors at the inner mitochondrial membrane (IMM) where it is processed by the rhomboid protease of the IMM, presenilin associated rhomboid-like protease (PARL) (Michiorri et al., 2010), and degraded by mitochondrial processing peptidases (Jin et al., 2010). However, when mitochondrial membrane potential is lost, PINK1 is not cleaved by PARL, and thus accumulates in the mitochondria (Jin et al., 2010).

Following accumulation of PINK1, the cytosolic E3 ubiquitin ligase PARKIN is recruited to the mitochondria, where it ubiquitinates various mitochondrial proteins (Geisler et al., 2010b; Narendra et al., 2010b; Vives-Bauza et al., 2010). Endogenous PARKIN has been shown to ubiquitinate mitochondrial localized MFN1 and MFN2 in both *Drosophila* and human cells (Gegg et al., 2010;Poole et al., 2010;Rakovic et al., 2011;Ziviani et al., 2010;Tanaka et al., 2010), while overexpressed PARKIN can also ubiquitinate VDAC (Voltage Dependent Anion Channel), components of the mitochondrial transport TOM complex, fission protein FIS1, pro-apoptotic protein BAK, mitochondrial movement Rho GTPases (MIRO) 1 and 2, and mitochondrial hexokinase (Yoshii et al., 2011;Chan et al., 2011;Okatsu et al., 2012;Sarraf et al., 2013). These ubiquitinated mitochondrial proteins can either be degraded by the proteasome, thus coordinating mitochondrial shape, cell metabolism, and mitochondrial movement with mitophagy, or be recognized by an LC3-and ubiquitin-binding autophagy adaptor protein p62/SQSTM1 thereby promoting mitophagy

(Tanaka et al., 2010;Geisler et al., 2010a;Lee et al., 2010;Narendra et al., 2010a). Recent studies provided evidence that PARKIN interaction with AMBRA1, PINK1 interaction with BECN1, or sterile α and TIR motif containing 1 (SARM1) and tumor necrosis factor receptor-associated factor 6 (TRAF6), may also play a role in mitophagy (Van et al., 2011;Michiorri et al., 2010;Murata et al., 2013). These studies suggest an essential role of PINK1 and PARKIN in mediating mitophagy of depolarized mitochondria (Fig.2).

In parallel with the PINK1/PARKIN pathway, DJ-1 is also involved in removal of damaged mitochondria (Thomas et al., 2011). DJ-1 levels increase at mitochondria following oxidative damage in both fibroblasts and neurons, with mitochondrial removal dependent on PARKIN and possibly PINK1 (Joselin et al., 2012). DJ-1 knockout neuroblastoma cells exhibit reduced mitochondrial membrane potential and increased mitochondrial fragmentation that is reversible upon treatment with glutathione (McCoy and Cookson, 2011). These models demonstrate the importance of key mitophagy genes in maintaining proper mitochondrial health and function, as well as preventing damage associated with an increased production of free radical species.

It should be noted that PINK1 and PARKIN translocation to damaged mitochondria either by direct depolarization or exposure to other mitochondrial toxins is highly dependent on cell type, levels of PINK1 and PARKIN expression, and growth conditions (Rakovic et al., 2013;Rakovic et al., 2010;Van, V et al., 2011;Cai et al., 2012;Vives-Bauza et al., 2010). Additional factors, including AF-6 (Haskin et al., 2013), and FBXO7 (Burchell et al., 2013), have been identified as regulating mitophagy by direct interactions with PARKIN.

Several Genome-wide screens have further identified other mitophagy regulators (Orvedahl et al., 2011;Lefebvre et al., 2013;Hasson et al., 2013). In a screen to detect genes required for virophagy, 96 were found to play a role in PARKIN-mediated mitophagy (Orvedahl et al., 2011). From this screen, functions of one particular protein, SMURF1 (SMAD specific E3 ubiquitin protein ligase 1 which encodes a HECT-domain ubiquitin ligase), have been validated in mouse knockouts as they accumulate damaged mitochondria in the heart, brain and liver (Orvedahl et al., 2011). Another independent screen has identified ATPIF1/IF1 (ATPase inhibitory factor 1) as promoting collapse of $\Delta\Psi$ and enabling PARKIN recruitment to the mitochondria and mitophagy by blocking ATPase activity (Lefebvre et al., 2013). A third genome-wide siRNA screen further identified factors, including TOMM7, SIAH7, HSPA1L and BAG4, that can either enhance or decrease PARKIN accumulation at the mitochondria (Hasson et al., 2013). Validation in additional cell lines confirmed that TOMM7 is not required for TOM-mediated general protein import, but plays an important role in anchoring PINK1 when $\Delta\Psi$ is depleted, in both HCT116 cells and in human iPSC derived tyrosine hydroxylase positive neurons. SIAH3 knockdown in BE(2)-M17 neuroblastoma cells increased both PINK1 accumulation and PARKIN translocation to depolarized mitochondria. Independent of PINK1 protein accumulation, HSPA1L enhances, whereas BAG4 prevents, PARKIN translocation to the mitochondria by direct interaction with PARKIN (Hasson et al., 2013).

Downstream of PARKIN activation, it has been found that TBC1D15, a mitochondrial Rab GTPase-activating protein (Rab-GAP), inhibits excessive Rab7 activity, and associates with

both the mitochondria through binding FIS1 and the isolation membrane through binding to LC3 family proteins (Yamano et al., 2014). In addition to TBC1D15, TBC1D17 interacts with FIS1 and TBC1D15, and facilitates TBC1D15 function (Yamano et al., 2014).

2.3 Mitophagy regulation by MTOR, mitochondrial membrane lipids and mitochondrial protein modifications

Recent studies have also identified additional mechanisms of mitophagy regulation in response to mtDNA damage, mitochondrial toxins, loss of iron, mitochondrial protein modification or viral infections. In bovine aortic endothelial cells, exposure to hemin led to mitochondrial dysfunction and activation of mitophagy (Higdon et al., 2012). In cybrid cells with a variety of pathogenic mtDNA mutations, loss of mitochondrial membrane potential alone could not trigger mitophagy. But when coupled with the inhibition of MTOR by rapamycin, mitophagy occurred (Gilkerson et al., 2012). In Akita$^{+/Ins2}$-derived β-cells, a mutation in the insulin 2 gene led to ER stress and mitochondrial damage, which was associated with increased DRP1 and decreased MFN1, p62 and PARKIN (Mitchell et al., 2013b). In primary human fibroblasts, iron chelation induced mitophagy, which was independent of PINK1 or PARKIN, but interestingly was dependent on glycolysis (Allen et al., 2013).

Starvation-induced PI3K/AKT activities block the translocation of DRAM to mitochondria by direct physical interactions between p-AKT and DRAM, thereby attenuating mitophagy (Liu et al., 2014). Additional factors, including HMGB1 and HSPB1 enable mitophagy, while the exact mechanism of their actions are yet to be defined (Tang et al., 2011). Interestingly, PINK1 can also engage mitophagy of energetically healthy mitochondria in response to expression of unfolded proteins in the mitochondrial matrix, or when LONP1, a mitochondrial protease, is knocked down (Jin and Youle, 2013). In addition, autophagosome-independent, PARKIN and PINK1-dependent lysosome-mediated degradation of mitochondria has been reported (McLelland et al., 2014).

In primary cortical neurons and SH-SY5Y cells, rotenone, staurosporine, and 6-hydroxydopamine caused externalization of the mitochondrial lipid cardiolipin to the mitochondrial surface, which is then recognized by LC3 to signal removal by mitophagy. When cardiolipin synthesis or transport is blocked by siRNA-mediated knockdown of cardiolipin synthase or phospholipid scramblase-3, mitochondria are no longer engulfed by the autophagosome, indicating that cardiolipin externalization is necessary for mitophagy in response to these toxins (Chu et al., 2013).

In HepG2 cells, siRNA mediated knockdown of GCN5L1, an essential component of the mitochondrial acetyltransferase program, leads to an increase of mitochondrial associated LC3-II, p62 and protein ubiquitination, as well as an increase of LAMP-1 colocalization with the mitochondria, and decreased mitochondrial mass and protein levels (Webster et al., 2013). The GCN5L1 knockdown induced mitophagy is dependent on SIRT3, ATG5 and p62, but not PARKIN (Webster et al., 2013). The whole cell levels of p-S6K, p62 and LC3-II/LC3-I are unchanged in response to GCN5L1 knockdown, indicating a specific effect on mitophagy (Webster et al., 2013). Interestingly, the increased mitophagy in response to

GCN5L1 depletion led to an increased resistance to mitochondrial stressors such as rotenone and paraquat (Webster et al., 2013).

3. Mitophagy in human diseases

Here we summarize evidence that mitophagy is important for mitochondrial quality control *in vivo*, and that mitophagic deficiencies exacerbate pathologies in disease situations, with a main focus on Parkinson's disease, cancer, heart and liver diseases (Table 1).

3.1 Mitophagy in Parkinson's disease

Mutations of mitophagy genes *PARKIN*, *PINK1*, and *DJ-1* have been associated with autosomal recessive Parkinson's disease (Trinh and Farrer, 2013;Lubbe and Morris, 2013). Mitochondrial dysfunction has also been reported in lymphoblasts carrying *DJ-1*mutations (Irrcher et al., 2010), fibroblasts carrying *PINK1* mutations (Abramov et al., 2011), and in induced pluripotent stem cell (iPSC)-derived neurons carrying *PARKIN* mutations (Imaizumi et al., 2012).

Pesticides that target the mitochondria, such as rotenone and paraquat, have been associated with increased risk of developing Parkinson's disease (Tanner et al., 2011). As discussed above in 2.3, rotenone induces mitophagy in SH-SY5Y cells and primary neurons, with externalization of cardiolipin acting as the signal to remove damaged mitochondria (Chu et al., 2013). Externalized cardiolipin is recognized and bound by LC3 to recruit mitochondria to the autophagosome (Chu et al., 2013). This mechanism of mitophagy is independent of mitochondrial depolarization, as well as PINK1 or p62 recruitment to the mitochondria, and may represent a more controlled removal mechanism for mitochondrial turnover (Chu et al., 2013). MPP^+, a metabolite of MPTP which induces *parkinsonism* in humans, has been shown to induce mitophagy in neuroblastoma SH-SY5Y cells in a MAPK, ATG5, ATG7, and ATG8 dependent, but BECN1 independent manner (Zhu et al., 2007).

3.2 Mitophagy in cancer

Mitochondrial quality control is important, as dysfunctional mitochondria may contribute to accumulation of reactive oxygen species (ROS) (Murphy, 2009), which can then damage nuclear and mtDNA, inducing genome instability and tumor initiation. In addition, mitophagy alteration in the host stromal microenvironment may also play a role in nutrient recycling and promotion of cancer growth. For example, cigarette smoke promotes DNA damage, autophagy and mitophagy in stromal fibroblasts, leading to the secretion of L-lactate and ketone bodies to support neighboring cancer cells to proliferate (Salem et al., 2013). Finally, significant alteration of levels of proteins that impact mitophagy has been found in various tumors.

PARKIN has been proposed as a tumor suppressor gene as it is mutated and down-regulated in different tumors, such as glioblastoma, breast cancer, ovarian cancer, sporadic colorectal cancer, hepatocellular carcinoma, and pancreatic tumors (Letessier et al., 2007;Fujiwara et al., 2008;Veeriah et al., 2010;Poulogiannis et al., 2010;Sun et al., 2013). Another mitophagy effector, PINK1, induced a decrease in cell growth in soft agar when overexpressed in MCF-7 cells (Berthier et al., 2011). *PINK1* mRNA expression has also been proposed to

serve as a survival prognostic marker in adrenocortical (ACT) tumors (de Reynies A. et al., 2009;Fragoso et al., 2012).

BNIP3 has been shown to be silenced in pancreatic cancer compared to normal tissue (Erkan et al., 2005;Okami et al., 2004). It has been proposed that BNIP3 and mitophagy protects cells against tumorigenesis by controlling intracellular levels of ROS, but when cells undergo a transformation event, the BNIP3 expression is lost. This leads to the accumulation of damaged mitochondria, increased ROS, genomic instability and progression to a more advanced stage of pancreatic cancer (Lu and Harrison-Findik, 2013). NIX/BNIP3L (BNIP3-like protein) expression is a factor of good prognosis for astrocytomas (AS, grade II). In hepatocellular carcinomas (HCC), BNIP3L and BNIP3 silencing has been linked to a poor prognosis (Calvisi et al., 2007). Interestingly, the silencing of these genes in these tumors has been correlated to hypermethylation.

GABARAPL1 ($GABA_A$ receptor associated protein like 1), one of the ATG8 homologues in mammals (Le Grand et al., 2011), has been shown to be associated with autophagosomes (Chakrama et al., 2010) and to interact with NIX to participate in the specific degradation of mitochondria in reticulocytes (Novak et al., 2010). It has also been demonstrated that GABARAPL1 expression is decreased in breast tumors and that a high expression of its mRNA is associated with a better outcome for lymph node-positive breast cancer patients (Berthier et al., 2010).

Mitochondrial fission is increased in human lung cancer cells (Rehman et al., 2012) and invasive breast carcinoma (Zhao et al., 2013). Impairment of fission in tumorigenic lung epithelial A549 cells decreased apoptosis, autophagy and mitophagy (Thomas and Jacobson, 2012). It should be noted that although mitophagy genes are frequently down-regulated in many tumors, and their activation has been shown to inhibit cancer cell proliferation or tumor growth in nude mice, few have directly tested whether tumorigenesis or tumor growth is directly linked to mitophagy. This will need to be investigated in future studies.

3.3 Mitophagy in diseases in the heart and liver

Heart failure, aging, cardiomyopathy, and ischemia-reperfusion injury are all associated with mitochondrial dysfunction, indicating that mitochondrial quality control through mitophagy may play an important role in limiting cellular damage (Dutta et al., 2012). Mice deficient in *Atg5* in the adult heart, *Bnip3* or *Nix*, accumulate damaged or dysfunctional mitochondria and develop cardiac dysfunction (Nakai et al., 2007;Dorn, 2010). Mice deficient in *Pink1* develop early onset cardiac hypertrophy (Billia et al., 2011). Recent studies also found that *Mfn2* deficiency in mouse cardiomyocytes prevented depolarization-induced PARKIN translocation to the mitochondria and suppressed mitophagy, leading to accumulation of morphologically and functionally abnormal mitochondria, and dilated cardiomyopathy (Chen and Dorn, 2013),

PARKIN is also important for survival in response to hemodynamic stress (Nakai et al., 2007). *Parkin* deficient mice exhibit decreased mitophagy, accumulation of dysfunctional mitochondria, and decreased survival after infarction (Kubli et al., 2013). Ischemia-induced mitophagy appears to involve BNIP3, and is inhibited by p53-mediated induction of TIGAR

(TP53-induced glycolysis and apoptosis regulator) (Hoshino et al., 2012). Doxorubicin-induced mitophagy has also been shown to depend on PARKIN and inhibited by cytosolic p53 binding to PARKIN (Hoshino et al., 2013). In response to ischemic preconditioning, PARKIN and p62 are translocated to the mitochondria, and PARKIN is required for cardioprotection (Huang et al., 2011). A cholesterol lowering drug, simvastatin, increased PARKIN translocation to the mitochondria, as well as loss of mitochondrial connectivity and membrane TOM70 protein in HL-1 cells. *In vivo*, simvastatin protected against coronary artery ligation induced infarct, and the protection was diminished in PARKIN deficient mice, suggesting that cardioprotection of simvastatin is mediated by PARKIN (Andres et al., 2013). Mitophagy may also be important to control inflammation, as a recent study reported that mtDNA that escaped from autophagy led to Toll-like receptor (TLR) 9-mediated inflammatory responses in cardiomyocytes, myocarditis and dilated cardiomyopathy (Oka et al., 2012).

In the liver, mitophagy contributes to mitochondrial loss and bioenergetic deficit in response to the environmental toxin cadmium, which is mediated by upregulation and translocation of DNM1L to the mitochondria, followed by mitochondrial fragmentation and colocalization of mitochondria with the lysosomes (Pi et al., 2013). It has also been suggested that MFN1 or MFN2-dependent mitochondrial spheroid formation is important for mitophagy in response to acetaminophen-induced liver injury and may play a role in compensatory proliferation of cells adjacent to the necrotic centrilobular area (Ni et al., 2013). BNIP3 deficiency also led to increased mitochondrial mass, increased mitochondrial populations with a loss of membrane potential, abnormal morphology, decreased mitochondrial function, and increased inflammation and steatohepatitis (Glick et al., 2012).

4 Conclusions/Future Directions

Targeted removal of mitochondria via mitophagy is essential in maintaining mitochondrial quality, cell viability and homeostasis. Understanding of mitophagic mechanisms and their regulation in different tissues and cells under healthy and stressed conditions will help us better understand disease pathogenesis and develop more effective therapeutic approaches.

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Organelle Facts

- Mitophagy is important for mitochondrial quality control
- Mitophagy is regulated by interactive adaptor proteins in the autophagy pathway
- Mitophagy is regulated by mitochondrial dynamics
- Mitophagy is regulated by mitochondrial depolarization, PINK1 and PARKIN
- Mitophagy dysregulation contributes to disease pathologies

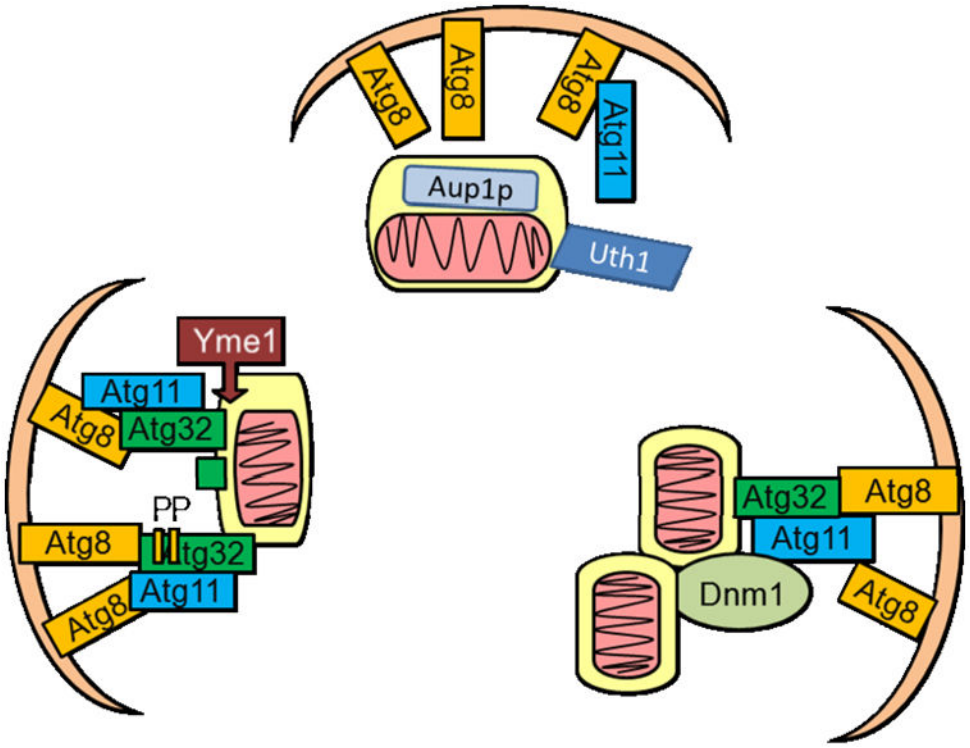

Figure 1. Adaptor proteins in mitophagy

In yeast, selective autophagy of mitochondria is mediated by mitochondrial targeted proteins such as Uth1, Aup1p, or Atg32. While the mechanisms of interaction between Aup1p and Uth1 and the autophagy machinery are still unclear, more is known regarding Atg32 function in mitophagy. Under starvation conditions, Atg32 localizes to the mitochondria and interacts with Atg8 and Atg11 to bring mitochondria to the autophagosome. Phosphorylation of Atg32 at Ser-114 and Ser-119, or cleavage of Atg32 by Yme1, facilitates its interaction with Atg11. Atg11 interaction with mitochondrial fission protein Dnm1 and recruitment of fission complex to the mitochondria are also required for mitophagy in response to nitrogen starvation.

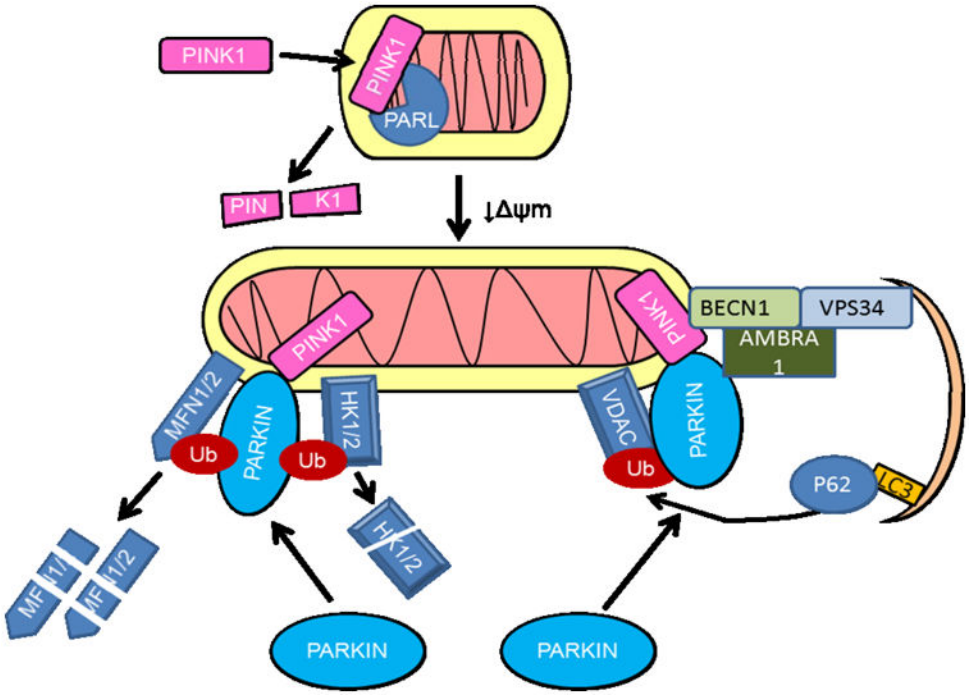

Figure 2. Mitophagy in response to loss of membrane potential

In healthy mitochondria PINK1 (PTEN – induced putative kinase 1) is targeted to the mitochondrial inner membrane where it is cleaved by the rhomboid protease of the IMM, presenilin associated rhomboid-like protease (PARL), and degraded. In stressed mitochondria with depleted membrane potential (↓Δψm), PARL is inactivated, and PINK1 accumulates in the mitochondria, recruiting the E3 ubiquitin ligase PARKIN. PARKIN can ubiquitinate Mitofusins 1 and 2 (MFN1 and 2), hexokinases, TOM complex components, FIS1, BAK, MIRO as well as VDAC. The ubiquitinated proteins are either degraded by the proteasome, or recognized by ubiquitin and LC3-binding autophagy adaptor protein p62/SQSTM1 which recruits them to autophagosomes. PARKIN-AMBRA1 interaction, or PINK1-BECN1 interaction can also facilitate mitophagy.

Table 1

Evidence that mitophagy is involved in Parkinson's disease, cancer, heart and liver diseases

Mitophagy dysregulation	Pathology	References
DJ-1 deficient PD patients	Mitochondrial dysfunction in lymphoblasts	(Irrcher et al., 2010)
PINK1 deficient PD patients	Mitochondrial dysfunction in fibroblasts	(Abramov et al., 2011)
PARKIN deficient PD patient	Mitochondrial dysfunction in iPSC-derived neurons	(Imaizumi et al., 2012)
PARKIN mutation or down-regulation	Glioblastoma, breast cancer, ovarian cancer, sporadic colorectal cancer, hepatocellular carcinoma, and pancreatic tumors	(Letessier et al., 2007;Fujiwara et al., 2008;Veeriah et al., 2010;Poulogiannis et al., 2010;Sun et al., 2013)
PINK1 mRNA expression	Survival prognostic marker in adrenocortical (ACT) tumors	(de Reynies A. et al., 2009;Fragoso et al., 2012)
GABARAPL1 down-regulation	breast tumors	(Berthier et al., 2010)
Impairment of fission	Tumorigenic lung epithelial A549 cells with decreased apoptosis, autophagy and mitophagy	(Thomas and Jacobson 2012)
Mice deficient in *Atg5* in adult heart, *Bnip3* or *Nix*	Accumulate damaged or dysfunctional mitochondria and develop cardiac dysfunction	(Nakai et al., 2007;Dorn 2010)
Mice deficient in *Pink1*	Early onset cardiac hypertrophy	(Billia et al., 2011)
Mfn2 deficiency in mouse cardiomyocytes	Decreased depolarization-induced PARKIN translocation to the mitochondria, suppressed mitophagy, accumulation of abnormal mitochondria, dilated cardiomyopathy	(Chen and Dorn 2013)
PARKIN	Involved in survival in response to hemodynamic stress, infarction, doxorubicin toxicity, and ischemia; as well as cardioprotection of simvastatin	(Nakai et al., 2007;Kubli et al., 2013;Huang et al., 2011;Hoshino et al., 2013;Andres et al., 2013)
DNM1L	Involved in mitophagic depletion of mitochondria in response to environmental liver toxin cadmium	(Pi et al., 2013).
MFN1 and MFN2	Involved in mitophagy in response to acetaminophen-induced liver injury and may play a role in compensatory proliferation of cells adjacent to the necrotic centrilobular area	(Ni et al., 2013)
BNIP3 deficiency	Increased mitochondrial mass, increased mitochondrial populations with a loss of membrane potential, abnormal morphology, decreased mitochondrial function, and increased inflammation and steatohepatitis	(Glick et al., 2012)