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REVIEW

Current opinions on mitophagy in fungi

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ABSTRACT

Mitophagy, as one of the most important cellular processes to ensure quality control of mitochondria, aims at transporting damaged, aging, dysfunctional or excess mitochondria to vacuoles (plants and fungi) or lysosomes (mammals) for degradation and recycling. The normal functioning of mitophagy is critical for cellular homeostasis from yeasts to humans. Although the role of mitophagy has been well studied in mammalian cells and in certain model organisms, especially the budding yeast *Saccharomyces cerevisiae*, our understanding of its significance in other fungi, particularly in pathogenic filamentous fungi, is still at the preliminary stage. Recent studies have shown that mitophagy plays a vital role in spore production, vegetative growth and virulence of pathogenic fungi, which are very different from its roles in mammal and yeast. In this review, we summarize the functions of mitophagy for mitochondrial quality and quantity control, fungal growth and pathogenesis that have been reported in the field of molecular biology over the past two decades. These findings may help researchers and readers to better understand the multiple functions of mitophagy and provide new perspectives for the study of mitophagy in fungal pathogenesis.

Abbreviations: AIM/LIR: Atg8-family interacting motif/LC3-interacting region; BAR: Bin–Amphiphysin–Rvs; BNIP3: BCL2 interacting protein 3; CK2: casein kinase 2; Cvt: cytoplasm-to-vacuole targeting; ER: endoplasmic reticulum; IMM: inner mitochondrial membrane; mETC: mitochondrial electron transport chain; OMM: outer mitochondrial membrane; OPTN: optineurin; PAS: phagophore assembly site; PD: Parkinson disease; PE: phosphatidylethanolamine; PHB2: prohibitin 2; PX: Phox homology; ROS, reactive oxygen species; TM: transmembrane.

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Introduction

The term "mitochondria", which is derived from the Greek words tubular "mitos" and punctate "chondrion", was originally used by Carl Benda in 1899 to describe its pluralistic dynamics [1]. In fact, mitochondria, which are a kind of subcellular organelles, were first observed in 1890 by Richard Altmann as refractive granules called "bioblasts" in fixed tissues [1,2]. As an organelle of oxidative phosphorylation, mitochondria are the primary sources and targets of reactive oxygen species (ROS), which cause significant damage to biologically-related molecules [3]. Three defense strategies against ROS include multiple proteases that degrade aggregated mitochondrial proteins at the molecular level, mitophagy at the organelle level to maintain mitochondrial quality and quantity, and apoptosis at the cell level to maintain mitochondrial balance and cell homeostasis [4–7].

Although the concept of "mitophagy" was first proposed in 2005, mitochondria have been observed in mammalian lysosomes since at least 1957 [8–10]. In 2009, the first mitophagy receptor was identified in *Saccharomyces cerevisiae*, named Atg32 [11,12], and fifteen mitophagy receptors were subsequently identified in mammalian cells, including BNIP3L/NIX (BCL2 interacting protein 3 like) [13,14], BNIP3 (BCL2 interacting protein 3) [15,16], FUNDC1 (FUN14 domain containing 1) [17–19], ceramide [20,21], cardiolipin [22,23], OPTN (optineurin) [24], AMBRA1 [25], SQSTM1/p62 [26], BCL2L13 (BCL2 like 13; a mammalian homolog of Atg32) [27], NBR1 (NBR1 autophagy cargo receptor) [28,29], CALCOCO2/NDP52 (calcium binding and coiled-coil domain 2) [30,31], TAX1BP1 (Tax1 binding protein 1) [32], RHOT1/MIRO1 (ras homolog family member T1) [33,34], FKBP8 (FKBP prolyl isomerase 8) [35,36], PHB2 (prohibitin 2) [37]; the mitophagy receptor Atg43 was identified in the fission yeast *Schizosaccharoyces pombe* in 2020 [38,39]. Mitophagy plays an important role in many diseases, such as neurodegenerative disorders, diabetes mellitus and Parkinson disease (PD) [40–44]. The identification of a series of mitophagy receptors located in the outer mitochondrial membrane (OMM) or inner mitochondrial membrane (IMM) provides a useful reference for studying the mechanism, physiological role, origin and evolution of mitophagy in eukaryotes.

Although the function of mitophagy in fungal pathogenesis has been indicated, the specific mechanisms of mitophagy-mediated interactions between pathogenic fungi and hosts remains largely unknown [45–49]. Currently, new evidence has shown that mitophagy is closely related to the

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mitochondrial electron transport chain (mETC), which consists of four multienzyme complexes, namely, complex I (NADH dehydrogenase), complex II (succinate dehydrogenase), complex III (bc_1 complex or cytochrome c reductase) and complex IV (cytochrome c oxidase), and is the key to energy production and organismal survival [50–53]. These studies can provide new clues for the search of mitophagy receptors. In this review, we summarized the biological functions of fungal mitophagy by comparing the similarities and differences in mammals, yeast and pathogenic fungi, and point out the possible regulatory pathways of mitophagy in plant pathogenic fungi, providing new inspiration for molecular biology research on these pathogenic organisms.

Occurrence of mitophagy

In response to environmental stress such as starvation, damage and ROS, eukaryotes typically trigger evolutionarily conserved macroautophagy (hereafter autophagy) to recover and degrade cytosolic components [54–57]. Autophagic cargoes, such as organelles and macromolecules, are essentially swallowed into double-membraned autophagosomes; the outer membranes of these transient compartments fuse with vacuoles or lysosomes to degrade these cargos, providing new metabolites for recycling and utilization [58–61]. In addition to nonselective autophagy, eukaryotes are also able to recycle different organelles in a targeted manner, called selective autophagy, such as mitophagy, endoplasmic reticulum (ER)-specific reticulophagy, and pexophagy [62–65]. Mitophagy is a process that selectively degrades damaged or excess mitochondria through the autophagy system, and its molecular mechanisms have been well studied in yeast and mammalian cells [66–69]. Although there is evidence that mitophagy can occur through either a macroautophagic or microautophagic process (the latter involving uptake at the limiting membrane of the vacuole, and hence independent of autophagosomes), the former has been best characterized and will be the focus of this review.

PINK1-PRKN pathway

The regulatory mechanism of ubiquitination/deubiquitination in mitophagy has been well studied in mammals, where the PINK1-PRKN/Parkin pathway is a typical mitochondrial quality control system involved in the selective clearance of unhealthy mitochondria [70–74]. PINK1 is a kinase in the OMM, and PRKN is a cytoplasmic E3 ubiquitin ligase [75,76]. Studies have shown that the accumulation of PINK1 in damaged mitochondria is a signal for PRKN to selectively degrade mitochondria. PINK1 activates PRKN by phosphorylating it at S65, enhancing the E3 ubiquitin ligase activity of PRKN and promoting its recruitment from the cytoplasm to the OMM [77–79]. Then, the activated PRKN binds to mitochondria and interacts with mitochondrial substrate proteins, resulting in multiple polyubiquitinated mitochondrial substrates. Many of the mitophagy receptors connect ubiquitinated mitochondria to an Atg8-family protein (comprised of the LC3 and GABARAP subfamilies in mammals) on the concave side of the phagophore, the precursor to the autophagosome [80–82]. Recent findings suggest that ubiquitination/deubiquitination-mediated mitophagy also exists in *S. cerevisiae*. The Ubp3-Bre5 deubiquitination complex is transferred to the mitochondria, which thereby inhibits mitophagy and activates other types of autophagy [83,84].

Receptor-mediated mitophagy

Receptor-mediated mitophagy is generally conserved from yeasts to humans and has been found in pathogenic fungi. At present, all of the identified selective autophagy receptors possess an LC3-interacting region (LIR) or Atg8-family interacting motif (AIM). The AIM or LIR motifs are characterized by W/F/Y-X-X-L/I/V sequences, in which X can be any acidic amino acid [85]. When selective autophagy is initiated, Atg8 is localized to the phagophore assembly site (PAS) after being covalently conjugated to phosphatidylethanolamine, and the mitophagy receptor interacts with Atg8 through its AIM/LIR motif to recruit the phagophore, which thereby promotes the selective isolation of a portion of the mitochondria [86–88]. After that, the core autophagy mechanism follows up to form autophagosomes which subsequently fuse with vacuoles or lysosomes to degrade the sequestered mitochondria, thereby controlling the quality and quantity of this organelle.

Although most mitophagy receptors, such as Atg32 and Atg43 in yeast and BNIP3L/NIX, BNIP3, FUNDC1, BCL2L13, and FKBP8 in mammalian cells, are located in the OMM. Researchers identified the mitophagy receptor PHB2 in the IMM of mammalian cells, which is a remarkable discovery that opens up new horizons for mitophagy research and receptor identification [37]. PHB2 contains a canonical LIR motif and is required as part of the PRKN-mediated mitophagy machinery. Wei *et al.* demonstrated that knockdown of *PHB2* prevents reductions in mitochondrial numbers after treatment with antimycin A and oligomycin in HeLa cells, which confirms that PHB2 deficiency results in defective mitochondrial clearance. PHB2 interacts with LC3 to recruit the phagophore membrane following OMM rupture. Overexpression of PHB2 promotes the recruitment of PRKN, whereas depletion of PHB2 activates PARL (an IMM-resident protease) to cleave PINK1; destabilized PINK1 prevents the recruitment of PRKN and, thus, PHB2 deficiency inhibits mitophagy [37].

In addition to the typical AIM/LIR motifs, well-organized mitophagy is regulated by phosphorylation, a crucial post-translational modification process, and multiple lines of evidence have shown that phosphorylation is a key event in receptor-mediated mitophagy [89–91]. In *S. cerevisiae*, the phosphorylation of the mitophagy receptor Atg32 depends on its N-terminal residues, Ser114 and Ser119, which are modified by casein kinase 2 (CK2), an evolutionarily highly conserved serine/threonine kinase that regulates a variety of cellular processes [92]. CK2 phosphorylation of Atg32 promotes its interaction with the scaffold protein Atg11, a common component in most types of selective autophagy including mitophagy. Accordingly, CK2 functional impairment leads to severe inhibition of mitophagy (Figure 1(b)) [93]. Recent studies have shown that the protein phosphatase 2A (PP2A)-like protein, Ppg1, cooperates with the Far

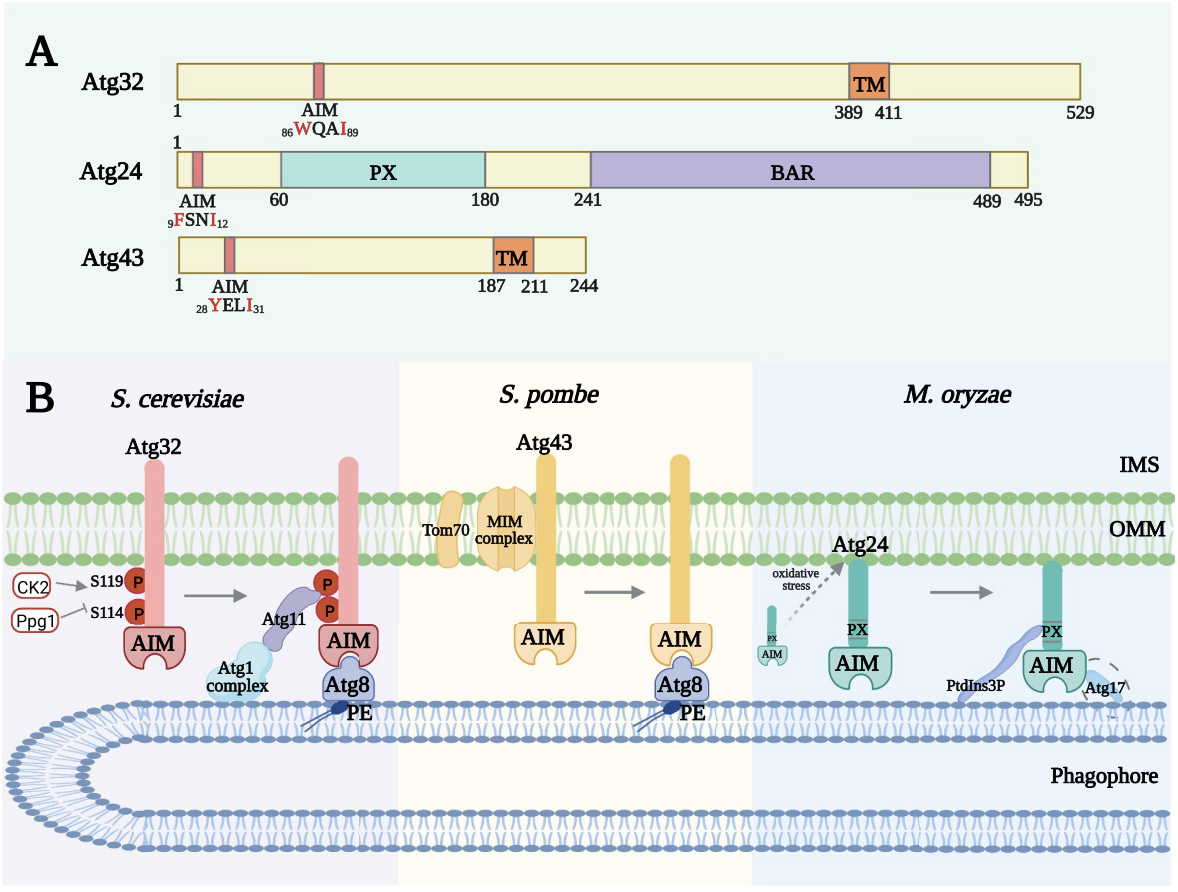

Figure 1. Receptor-mediated mitophagy in fungi. (A) Structural diagram of the mitophagy receptors in fungi. All three mitophagy receptors contain an AIM domain, the Atg8-family interacting motif (red). Atg32 and SpAtg43 contain a transmembrane (TM) domain for localization (dark purple). MoAtg24 contains a PX domain (light purple) and BAR domain (light red) for localization, and the PX domain is also used to interact with PtdIns3P. The protein sizes are expressed as the numbers of amino acids. (B) Models of mitophagy receptor localization, activation and action. The mitophagy receptor Atg32 of *S. cerevisiae* is regulated by phosphorylation and dephosphorylation. Atg32 is phosphorylated and activated by CK2 to recruit the autophagy scaffold protein Atg11 and interacts with Atg8 through the AIM motif to recruit the phagophore membrane to selectively enwrap mitochondria for degradation. The mitophagy receptor Atg43 of *S. pombe* is located in the OMM through the mitochondrial input factor MIM complex, and the mitochondrial input factor Tom70 surrounds and degrades mitochondria by recruiting the core autophagy machinery through the AIM motif. The mitophagy receptor Atg24 of *M. oryzae* is located in mitochondria via the PX and BAR domains, and interacts with PtdIns3P on the membrane through the PX domain. The *S. cerevisiae* homolog of Atg24, Snx4, can interact with Atg17.

complex (Far3, Far7, Far8, Vps64/Far9, Far10, and Far11) to dephosphorylate Atg32 by competing with CK2 for phosphorylation sites under non-mitophagy-inducing conditions, thereby inhibiting mitophagy. In Ppg1-depleted cells, the interaction between Atg32 and Atg11 is increased even under non-mitophagy-inducting conditions, which thus accelerates mitochondrial degradation [93].

Mitophagy in yeast

S. cerevisiae follows two basic metabolic pathways, the aerobic pathway and anaerobic pathway, which can be promoted by adding different carbon sources to the culture media [94]. When yeast cells grow to the quiescent stage or under nitrogen starvation condition, in particular following growth on a non-fermentable carbon source, mitophagy is induced [11,65,95,96]. Mitophagy helps to reduce oxidative stress, maintain mitochondrial morphology and genomic stability, improve tolerance to ethanol and protect cells during respiratory growth and heat-induced stress in yeast [97–99]. At present, two mitophagy receptors have been identified in yeast, namely Atg32 in the budding yeast *S. cerevisiae* and SpAtg43 in the fission yeast *S. pombe* [12,39,100].

Atg32 in S. cerevisiae

In 2009, the first recognized mitophagy receptor of yeast, Atg32, was identified in two laboratories through similar strategies and it was shown that this mitochondria-anchored protein is essential for mitophagy but is dispensable for other types of selective and nonselective autophagy, as well as the Cvt pathway [11,12] (Table 1). Atg32 is 59 kDa and consists of three essential modules: an N-terminal cytoplasmic domain (amino acid residues 1–388), a single transmembrane (TM) domain (amino acid residues 389–411), and a C-terminal intermembrane space (IMS) domain (amino acid residues 412–529) (Figure 1(a)) [11,12]. Among them, the TM domain is necessary for Atg32 to anchor to the OMM, and Atg32 is dispersed throughout the cytoplasm and nucleus in the absence of the TM domain. The N-terminal cytoplasmic domain contains the AIM motif, which is critical for Atg32 to interact with Atg8, and its mutation results in partial

Table 1. Mitophagy receptors in fungi and mitophagy regulators in pathogenic fungi.

Gene	Species	Phenotype	Functions	References
Mitophagy receptors				
ScATG32	*Saccharomyces cerevisiae*	Blocked mitophagy	Interacts with Atg8 and Atg11 to recruit phagophores	[11,12]
MoATG24	*Magnaporthe oryzae*	Blocked mitophagy, impaired growth and conidiation	Regulates mitophagy in foot cells	[45]
SpATG43	*Schizosaccharomyces pombe*	Blocked mitophagy, impaired growth	Interacts with Atg8 to recruit phagophores	[38,39]
Other regulatory factors				
AoATG11	*Aspergillus oryzae*	Mitochondria accumulate in cytoplasm	Involved in mitophagy and pexophagy	[115]
AcATG11	*Acremonium chrysogenum*	Blocked mitophagy and pexophagy	Involved in selective autophagy and nonselective autophagy	[116]
MoDNM1	*M. oryzae*	Impaired growth, virulence and appressorium formation	Involved in mitochondrial morphology and mitophagy	[46]
MoFIS1	*M. oryzae*	Impaired conidiation and virulence	Involved in mitochondrial morphology and mitophagy	[46,124]
MoMDV1	*M. oryzae*	Impaired conidiation and virulence	Involved in mitochondrial morphology and mitophagy	[46]
BbDNM1	*Beauveria bassiana*	Impaired growth and virulence and asexual development	Regulates mitochondrial fission and mitophagy	[126]
BbFIS1	*B. bassiana*	Impaired growth and virulence and asexual development	Regulates mitochondrial fission and mitophagy	[126]
BbMDV1	*B. bassiana*	Impaired growth and virulence and asexual development	Regulates mitochondrial fission and mitophagy	[126]
MoMSN2	*M. oryzae*	Impaired infectious growth	Controls mitophagy and mitochondrial morphology	[48]
MoAUH1	*M. oryzae*	Impaired infectious growth	Controls mitophagy and mitochondrial morphology	[48]
MoWHI2	*M. oryzae*	Reduced conidiation and virulence	Regulates mitophagy in foot cells and invasive hyphae	[49]
CaMCP1	*Candida albicans*	Impaired growth and virulence; accumulated mitochondria	Regulates mitophagy and maintains mitochondrial function	[105]

defects in mitochondrial degradation. When mitophagy is induced, Atg32 is activated at the transcriptional level and accumulates in the OMM, recruiting the phagophore to surround mitochondria by interacting with Atg11 and Atg8 and promoting the formation of autophagosomes (Figure 1(b)) [101,102]. The deletion of *ATG32* leads to complete inhibition of mitophagy, and overexpression increases mitophagy activity, which indicates that Atg32 is a specific rate-limiting factor that regulates the number of mitochondria to be degraded [11].

SpAtg43 in S. pombe

In 2020, the second recognized mitophagy receptor in yeast, SpAtg43, was identified in *S. pombe* [39] (Table 1). SpAtg43 is 27 kDa, similar to Atg32, and contains three essential modules, namely, the N-terminal cytoplasmic domain (amino acid residues 1–184), C-terminal IMS domain (amino acid residues 225–244), and single-TM domain (amino acid residues 187–211), for anchoring in mitochondria, respectively (Figure 1(a)). SpAtg43 is localized in the OMM through the Mim1-Mim2 complex and interacts with SpAtg8 [38,103]. Artificially linking SpAtg8 to mitochondria enables mitophagy without SpAtg43, which suggests that the main role of SpAtg43 in mitophagy is to stabilize phagophore expansion on mitochondria by interacting with SpAtg8 (Figure 1(b)). In addition, mutations in the AIM motif of SpAtg43 completely inhibit mitophagy, which suggests that mitophagy in *S. pombe* is highly dependent on AIM-mediated SpAtg43-SpAtg8 interactions. Interestingly, SpAtg43 shares no sequence homology with Atg32 in *S. cerevisiae* or the mitophagy receptor BCL2L13 in mammals. This may be due to SpAtg43 acquiring the function of the mitophagy receptor through convergent evolution, because SpAtg43 also plays a role in regulating growth [38,39]. These findings provide new insights into the regulatory mechanisms of mitophagy and the search for mitophagy receptors in other fungi.

Mitophagy in pathogenic fungi

Although the important role of mitophagy in mammalian cells and yeast has been confirmed, its crucial function in pathogenic fungi has not been revealed until the last decade. The Naqvi laboratory found that mitophagy is indispensable in the pathogenicity of the rice blast fungus *Magnaporthe oryzae*, indicating that mitophagy plays an indispensable role not only in the regulation of mitochondrial quality and quantity but also in maintaining pathogenic fungal virulence [45]. Later, the important role of mitophagy on pathogenicity was also confirmed in the opportunistic pathogenic fungus *Candida albicans*. Mcp1, a mitochondrial outer membrane protein, plays an important role in mitochondrial lipid homeostasis of yeast [104]. In *C. albicans*, Mcp1 is essential for mitophagy and mitochondrial function [105]. Deletion of *CaMCP1* blocked mitophagy, resulting in abnormal mitochondrial accumulation. In addition, the hyphae growth and virulence of Δ*Momcp1*mutants are impaired, but the principle of mitophagy affecting virulence has not been clarified [105] (Table 1).

M. oryzae has a complex infection cycle, including mycelial growth, conidia production, germ tube germination, appressorium formation and plant infection, which makes it a model organism for studying the interactions among pathogenic fungi and host plants [106–109]. The germ tube germinates from the apical cell of the three-cell conidium, and then the tip of the germ tube swells to form a special dome-shaped

infection structure, the appressorium. The mature appressorium has a dense outside melanin layer, with a large amount of accumulated glycerol inside, which results in a mechanical pressure of up to 8.0 MPa, which pierces the plant cells through the penetration peg [110]. *M. oryzae* has typical characteristics in its growth, development and infection mechanism and has high genetic operability, which has great advantages in studying pathogenic mechanisms. In *M. oryzae*, the transcription factor MoMsn2 regulates the expression of *MoAUH1*, and deletion of *MoMSN2* or *MoAUH1* leads to dysfunctional mitophagy, impaired mitochondrial morphology, and impaired growth of infection hyphae [48]. However, its potential mechanism in pathogenesis has not been clarified. Recent studies have shown that Δ*Mowhi2* mutants exhibit significantly reduced pathogenicity. Deletion of *MoWHI2*, on the one hand, leads to interrupted mitophagy in the foot cells (connect aerial hyphae with vegetative mycelia), resulting in reduced conidiation; on the other hand, leads to blocked mitophagy in the invasive hyphae, resulting in reduced virulence [49]. In this section, we focus on the factors affecting mitophagy in pathogenic fungi and the distinct roles of mitophagy in sporulation, mitochondrial quality control and pathogenicity.

Atg24 in M. oryzae

In 2013, researchers identified a sorting nexin associated with yeast Snx4/Atg24 as MoAtg24 in *M. oryzae*, which is the first studied mitophagy receptor in pathogenic fungi [45] (Figure 1(a)). Deletion of the corresponding gene blocks mitophagy in foot cells, leading to a high reduction in aerial hyphae and conidia, but has no effect on autophagy or pexophagy. MoAtg24 colocalizes with mitochondria under starvation or oxidative stress, which may directly recruit mitochondria into autophagic structures during mitophagy. Although lacking the typical TM domain of mammalian and yeast mitophagy receptors, MoAtg24 has a PX (Phox homology) domain and BAR (Bin-Amphiphysin-Rvs) domain that are required for mitochondrial localization, and deletion of the PX domain leads to cytoplasmic localization. Under oxidative stress conditions, mitochondrial targeting of MoAtg24 may be mediated by PX-phosphatidylinositol-3-phosphate (PtdIns3P) on the mitochondrial membrane [45]. In addition, the yeast homolog of MoAtg24 interacts with Atg17 (a component of the Atg1 kinase complex) to initiate autophagosome formation, and the W/F/Y-X-X-L/I/V motif is also found at the N terminus of MoAtg24 (Figure 1(b)) [45].

Based on the above comparisons, the potential mechanism of cargo selection during mitophagy appears to be conserved among unicellular yeast, filamentous fungi, and mammals: a mitochondrial localized receptor can interact with an Atg8-family protein and recruit the necessary core autophagy machinery on the surface of the phagophore (Figure 2(b)). However, this mitophagy model is obviously too simplistic in the complex biological activity regulation mechanism. Due to the general importance of mitophagy in eukaryotes, future research on mitophagy may need to transcend this established paradigmatic rule and discover new modes of mitophagy regulation. On the basis of exploring the commonness of mitophagy from yeast to mammals, researchers should further examine the differences in the regulatory mechanism of mitophagy in different eukaryotes from an evolutionary perspective.

The autophagic scaffold protein Atg11 in pathogenic fungi

A large number of studies over the years have shown that Atg11 is a common protein in most types of selective autophagy, and its function in pathogenic fungi has also been studied in recent years [111–114]. In 2015, Tadokoro and colleagues identified Atg11 in *Aspergillus oryzae* and explored

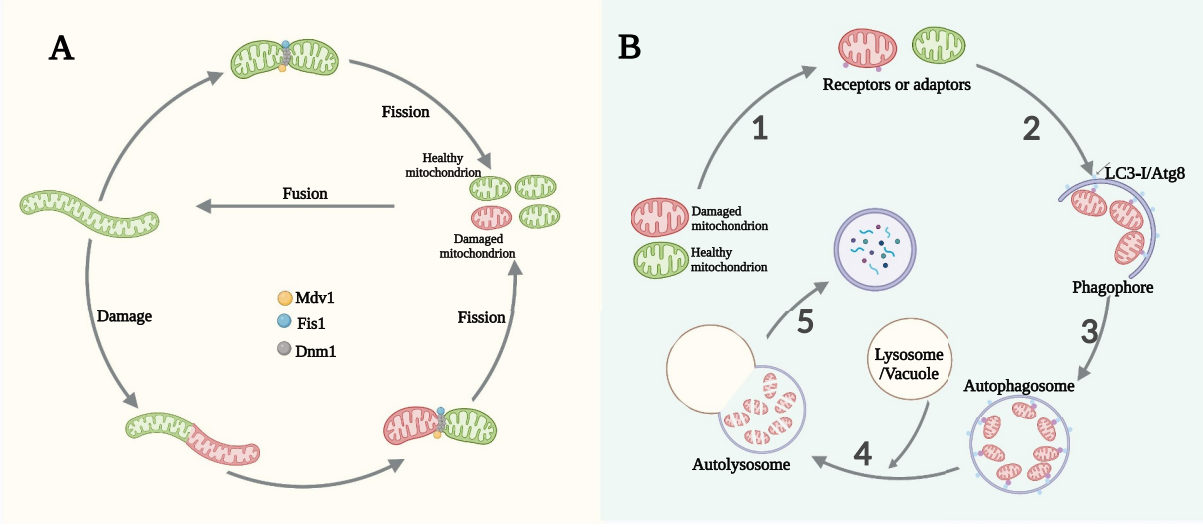

Figure 2. Models for regulating mitochondrial morphology and mitophagy in eukaryotes. (A) Schematic diagram of mitochondrial fission and fusion. Mitochondria usually take on various forms, and fission usually occurs before mitophagy. Fragmented mitochondria that are divided from healthy or damaged mitochondria can be recovered and degraded through mitophagy to thereby achieve the quantity and quality control of mitochondria. (B) Schematic diagram of the mitophagy process. 1. Activation of mitophagy receptors on the mitochondrial surface or recruitment of adaptors that mediate ubiquitin-mediated autophagy. 2. Recruit the phagophore by interacting with the core autophagy machinery. 3. Mitochondria to be degraded are sequestered within autophagosomes. 4. Fusion with vacuoles or lysosomes. and 5. Excess and damaged mitochondria are degraded and the breakdown products are released back into the cytosol for reuse.

its function in autophagy by means of gene knockout and fluorescence observations [115]. AoAtg11 colocalizes with the core autophagy protein AoAtg8, and is essential for mitophagy and pexophagy but is dispensable for nonselective autophagy and the Cvt pathway. Compared with the wild type, more undegradable mitochondria accumulate in the cytoplasm of *ΔAoatg11* mutants, suggesting that AoAtg11 is involved in mitophagy. However, mitochondrial fluorescence is also observed in the vacuoles of Δ*Aoatg11* mutants after 40 h; this is the result of long-term nutrient depletion, which leads to the induction of nonselective autophagy and nonselective sequestration of mitochondria. Furthermore, Atg11 also plays a role in various types of autophagy in another fungus, *Acremonium chrysogenum*. In *ΔAcatg11* mutants, conidiation significantly increases, cephalosporin production significantly decreases, mitophagy and pexophagy are blocked, and nonselective autophagy and the Cvt pathway are also blocked [116]. Although a previous study found that deletion of Atg11 in *M. oryzae* did not lead to a significant defect in pathogenicity [117], a recent study found that overexpression of Atg11 can promote fungus infection in an autophagy-related way [117], indicated that the Atg11 related network in autophagy is indeed essential for virulence of the rice blast fungus. In summary, studies on Atg11 in different species indicate that its important function in selective autophagy is beyond doubt, but its functional differences in various types of autophagy remain to be explored.

Mitophagy and mitochondrial fission

As mentioned above, mitochondria are dynamic organelles, and their morphologies are not invariable but constantly change in tubular and punctate/vesicular patterns to meet the requirements for their functioning and energy regulation. Numerous studies have shown that a series of conserved dynamins and dynamin-related proteins (DRPs) regulate mitochondrial morphology by regulating the balance between mitochondrial fission and fusion, which are critical for mitophagy [118–121]. Dynamins are large GTPase superfamily proteins containing five domains, namely, the GTPase domain, PLEK (pleckstrin) homology domain (PH), middle domain, proline-rich domain (PRD) and GTPase effector domain (GED), while DRPs lack one or more of these domains or have other domains [122]. Dynamins and DRPs are involved in a variety of cellular processes, which include pathogen resistance, mitochondrial fission and fusion, vacuolar fission, cytokinesis and plant cell membrane fission [122,123]. The functions of the DRPs, Dnm1, Fis1 and Mdv1, and their mechanisms in regulating mitochondrial morphology have been well studied in model organisms such as *S. cerevisiae, M. oryzae* and *Beauveria bassiana* (Figure 2(a)). Consistent with *S. cerevisiae*, MoDnm1, MoFis1 and MoMdv1 localize to mitochondria and peroxisomes and are required for complete virulence for the rice blast fungus *M. oryzae*; the Δ*Modnm1*, Δ*Momdv1* and Δ*Mofis1* deletion mutants show reduced growth, reduced conidiation, defective formation of punctate/vesicular mitochondria and delayed mitophagy [46].

An accurate filamentous-punctate-filamentous cycle of mitochondrial morphology has been found during the *Magnaporthe*-rice interaction [47]. Deletion of either MoDnm1 or MoFzo1 results in disruption of mitochondrial dynamics, which results in a significant reduction in pathogenicity. In the plant pathogen *Ustilago maydis*, UmDnm1 regulates mitochondrial fission, and deletion of the corresponding gene significantly weakens fungal virulence [125]. BbFis1, BbMdv1 and BbDnm1 also play a similar role in mitochondrial division and mitophagy, but the three fission-related gene products play different roles in the fungal development and virulence of *B. bassiana* [126].

The above studies show that Dnm1, Fis1 and Mdv1 play an important role in the regulation of mitochondrial fission, which thereby affects mitophagy (Table 1). However, many questions remain concerning the role of fission in mitophagy. For example, Dnm1 facilitates mitophagy in *S. cerevisiae*, but is not absolutely required for this process [111,127,128]. In the studies showing a defect in mitophagy in the absence of DRPs, is the blocked mitophagy only caused by blocked mitochondrial fission, or is it caused directly by dysfunctional regulation of dynamins in mitophagy? In general, although the main mechanism of mitochondrial fission is evolutionarily conserved in fungi, its role in pathogenic fungi is still poorly understood, and the mechanisms and specific regulatory processes of mitophagy in pathogenic fungi still need to be determined through additional studies.

Mitochondrial respiratory chain complex and mitophagy

The mitochondrial electron transport chain in eukaryotes consists of four multienzyme complexes, including complex I (NADH dehydrogenase), complex II (succinate dehydrogenase), complex III (bc_1 complex or cytochrome c reductase), and complex IV (cytochrome c oxidase), which are key to energy production and organismal survival [53,129–131]. In *S. cerevisiae*, complex III consists of 11 subunits and requires 13 assembly factors to assist in its correct assembly, which is a prerequisite for the normal operation of the sophisticated respiratory chain [132,133]. In recent years, increasing evidence has shown that complex III is closely related to autophagy in addition to being part of the mitochondrial respiratory chain (Figure 3). Researchers found that human glioblastoma H4 cells treated with a complex III inhibitor (antimycin A or myxothiazol) have decreased levels of LC3-II and blocked autophagy independent of ATP, ROS levels and membrane potential, but this treatment does not affect the autophagy regulatory pathways such as the MTOR-class I phosphoinositide 3-kinase signaling pathway [134]. In addition, complex III regulates the activity of HIF1A, which in turn regulates the expression of BNIP3, a mammalian mitophagy receptor, thereby promoting mitophagy [135–137]. Furthermore, the increased levels of reduced cytochrome b (the core subunit of complex III) and elevated levels of mitophagy components are necessary to trigger autophagy in *S. cerevisiae*. Therefore, increased levels of reduced cytochrome b may be the first signaling molecule through which complex III regulates autophagy or mitophagy [51]. In the

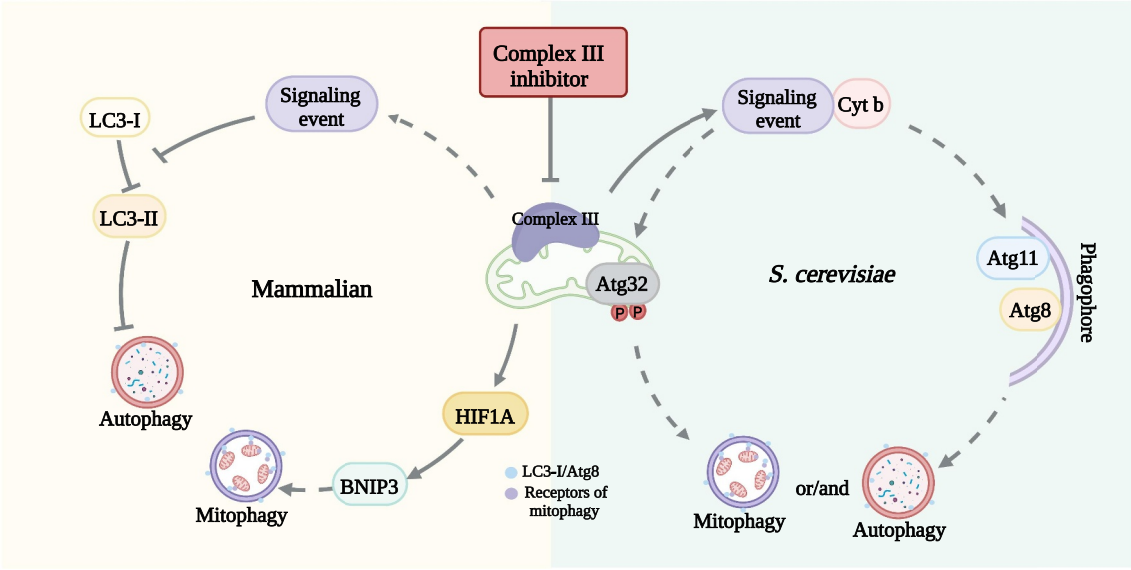

Figure 3. Possible models of respiratory chain complex III and related factors regulating mitophagy and autophagy. Inhibitors of respiratory chain complex III, antimycin A, myxothiazol and KCN, regulate mitophagy or autophagy in mammalian cells and in *S. cerevisiae* cells. In MEFs, the addition of antimycin A reduces the LC3-II levels and inhibits autophagy. Complex III regulates the activity of HIF1A, which regulates the expression of BNIP3, a mammalian mitophagy receptor, and promotes autophagy. In *S. cerevisiae* cells, the exogenous complex III inhibitor antimycin A or KCN induces autophagy, and the increased level of reduced cytochrome b may be the first signaling molecule in this pathway.

study of autophagy in *S. cerevisiae*, researchers also found an interesting phenomenon: *atg1Δ, atg5Δ, atg8Δ* and *atg12Δ* mutants exhibit mitochondrial dysfunction, such as growth defects, low membrane potential and accumulation of defective mitochondria. These findings argue that autophagy plays a key role in the maintenance of mitochondria, and defects in autophagy impair mitochondrial function [50]. The above findings strongly suggest that complex III has a regulatory role in autophagy that needs to be explored. Combined with the special location of the mitochondrial respiratory chain, the functional exploration of complex III-related subunits and assembly factors may provide new inspiration for the study of mitophagy in pathogenic fungi and even all eukaryotes.

Conclusions and perspectives

In the nearly 17 years since mitophagy was first proposed, it has been determined that its presence in many eukaryotic organisms is a universally conserved biological process. Mitophagy is affected and regulated by mitophagy receptors, mitochondrial fission and fusion, phosphorylation and ubiquitination/deubiquitination. This process plays an important role in the molecular regulation pathway in yeast, neurodegenerative diseases in mammals, mitochondrial clearance during erythrocyte maturation, paternal mitochondrial clearance in *Caenorhabditis elegans* embryos and the virulence of pathogenic fungi [138,139]. *M. oryzae*, as the pathogenic fungus with the most research related to mitophagy, is a wonderful model to be used as the basis of molecular biology research and to provide new perspectives for the mechanism of mitophagy in pathogenesis. Furthermore, some proteins have dual or multiple functions and participate in mitophagy and other types of autophagy or regulate other pathways. In addition to the identification of mitophagy receptors, the identification of mitophagy regulatory factors with multiple identities is also of great significance to the study of mitophagy.

One key premise of mitophagy is the accurate identification of damaged/dysfunctional mitochondria, so how does the organism identify and distinguish the mitochondria to be degraded? This has been a hot issue in the research field of mitophagy regulation mechanisms in recent years. Although this issue has been intensively studied in mammalian cells, there are still many questions to be further studied that are related to pathogenic fungi. In addition to receptor mediated mitophagy, is there receptor-independent ubiquitination-mediated mitophagy? Does the recognition of damaged mitochondria in pathogenic fungi involve a sequence of events in the OMM and IMM? What is the role of IMM proteins in mitophagy? As the core component of productive organelles, the mitochondrial respiratory chain complex shows a close relationship with mitophagy; are there any receptor components or regulatory factors that mediate mitophagy among these respiratory chain-related factors? There is also the question of how the core autophagy components other than Atg8 are recruited. The *S. cerevisiae* Atg19 and Atg34 receptors as well as the *Homo sapiens* OPTN, SQSTM1/p62 and CALCOCO2/NDP52 receptors interact with the E3-like Atg12–Atg5-Atg16/ATG12–ATG5-ATG16L1 complex [140,141]. Atg19 can directly interact with Atg5 through its AIM motif to recruit Atg12–Atg5-Atg16 to the prApe1 cargo [140,141]. A question worth exploring is whether this recruitment pattern is generally conserved and whether there are similar receptors for mitophagy.

A key challenge in plant-pathogen interactions is the precise regulation of mitophagy by pathogenic fungi at different stages, which we think is particularly interesting during pathogen invasion, as the role of mitophagy in pathogen expansion within the host remains unknown. Currently, drug targeting and protein crystallization methods are being used to study mitophagy-related regulatory factors in *M. oryzae*, and the identification of

new pathways or receptors and regulatory factors will help elucidate the processes and functions of mitophagy in plant-pathogen interactions and provide new methods for crop disease control. These studies will be extremely fascinating.

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Data availability statement

Data sharing not applicable-no new data generated.

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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