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MINI-REVIEW

Self-eating to grow and kill: autophagy in filamentous ascomycetes

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Abstract Autophagy is a tightly controlled degradation process in which eukaryotic cells digest their own cytoplasm containing protein complexes and organelles in the vacuole or lysosome. Two types of autophagy have been described: macroautophagy and microautophagy. Both types can be further divided into nonselective and selective processes. Molecular analysis of autophagy over the last two decades has mostly used the unicellular ascomycetes *Saccharomyces cerevisiae* and *Pichia pastoris*. Genetic analysis in these yeasts has identified 36 autophagy-related (*atg*) genes; many are conserved in all eukaryotes, including filamentous ascomycetes. However, the autophagic machinery also evolved significant differences in fungi, as a consequence of adaptation to diverse fungal lifestyles. Intensive studies on autophagy in the last few years have shown that autophagy in filamentous fungi is not only involved in nutrient homeostasis but in other cellular processes such as cell differentiation, pathogenicity and secondary metabolite production. This mini-review focuses on the specific roles of autophagy in filamentous fungi.

Keywords Autophagy · Filamentous ascomycetes · Pathogenicity · Heterologous protein production · Secondary metabolites

Introduction

Autophagy (literally, self-eating) is a conserved recycling process found in all eukaryotic cells. In autophagy, surplus, aberrant or defective cell constituents are degraded within vacuoles or lysosomes to achieve nutrient homeostasis under stress conditions or during developmental transitions (Nakatogawa et al. 2009; Yang and Klionsky 2009) (Fig. 1). The self-eating can be divided into macro- and microautophagy and can be either a nonselective or a selective process. Nonselective macroautophagy is the random engulfment of cytoplasm containing organelles into double-membraned vesicles called autophagosomes with delivery of the cargo to the vacuole for degradation. Microautophagy is the direct engulfment of cytoplasm or organelles by invaginations of the lysosomal or vacuolar membrane (Li et al. 2012). The selective degradation of organelles such as peroxisomes, mitochondria, ribosomes, nuclei and the ER are termed pexophagy, mitophagy, ribophagy, nucleophagy and reticulophagy, while the specific degradation of protein aggregates and bacteria is called aggrephagy and xenophagy (Jo et al. 2013; Lamark and Johansen 2012; Suzuki 2013). In addition, a cytoplasm-to-vacuole targeting (Cvt) pathway that operates under nutrient-rich conditions has been described. Under nonstarvation conditions, the Cvt pathway selectively transports hydrolytic enzymes such as aminopeptidase I (Ape1) and α-mannosidase (Ams1) to the vacuole (Khalfan and Klionsky 2002; Meijer et al. 2007). This pathway has been intensively studied in yeast, but has only been once described for filamentous ascomycetes (Yanagisawa et al. 2013).

Molecular analyses of autophagy have been mostly performed in the unicellular budding yeast *Saccharomyces cerevisiae* and in *Pichia pastoris* (Dunn et al. 2005; Nakatogawa et al. 2009; Ohsumi 2001; Reggiori and Klionsky 2013). In filamentous ascomycetes, autophagy has been intensively investigated in *Podospora anserina*, *Sordaria macrospora*, *Aspergillus oryzae* and the plant pathogen *Magnaporthe oryzae* (Table 1). Other reviews mainly summarize the role of macroautophagy in fungal development and pathogenicity (Bartoszewska and Kiel 2011; Khan et al.

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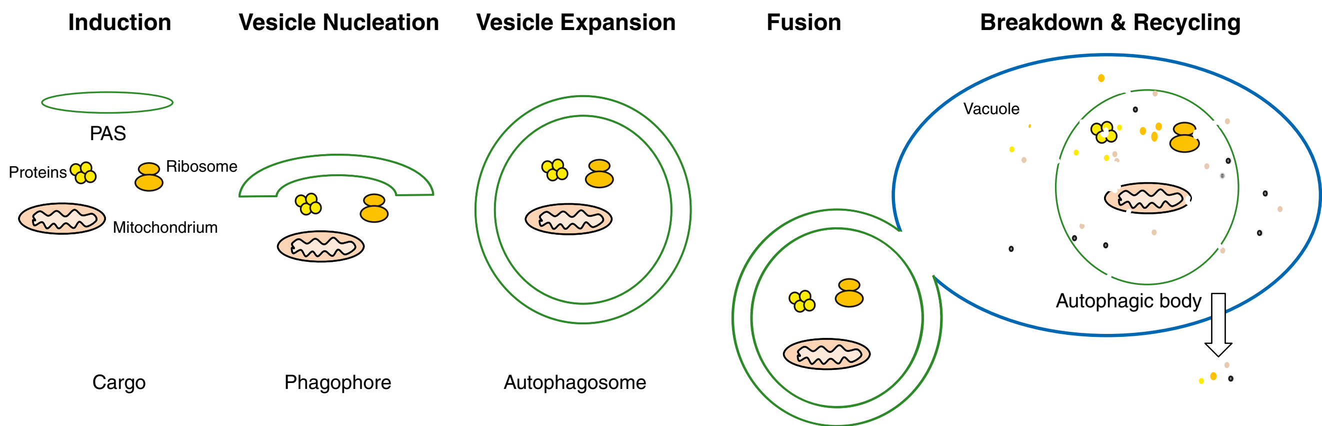

Fig. 1 Five sequential steps of autophagy based on findings in *S. cerevisiae*. After induction of autophagy, an initial sequestering phagophore is assembled at the phagophore assembly site (*PAS*). Expansion and curvature of the phagophore leads to the engulfment of the cargo (cytoplasm containing proteins and organelles) into the double-membraned autophagosome. Fusion of the autophagosomal outer membrane with the vacuolar membrane results in the release of the autophagic body which is surrounded by the inner autophagosomal membrane. Autophagic bodies and the sequestered cargo are broken down by hydrolytic enzymes. Finally, the breakdown products are exported into the cytoplasm for re-use

2012; Palmer et al. 2008; Pollack et al. 2009). This review focuses on recent advances in our understanding of autophagy in filamentous ascomycetes, including a description of the essential autophagic machinery, autophagy of organelles, the role of autophagy in pathogenicity as well as in heterologous protein and secondary metabolite production.

Molecular mechanisms of autophagy

Genetic analysis of yeasts identified 36 autophagy-related (*atg*) genes, of which 17 are required for all autophagy-related pathways and 19 are involved in selective autophagy or the induction of specific autophagy-related pathways in response to different physiological conditions and in selective autophagy (Inoue and Klionsky 2010; Motley et al. 2012; Nazarko et al. 2011; Suzuki et al. 2010). Genome mining of the published sequence of the filamentous ascomycete *S. macrospora* (Nowrousian et al. 2010), provides evidence for the presence of the 17 core *atg* genes (our unpublished results). Similar to the genomes of other filamentous ascomycetes (Kiel and van der Klei 2009; Meijer et al. 2007), the *S. macrospora* genome encodes only a few clear orthologs of the *S. cerevisiae* Atg proteins that are required for selective autophagy (Fig. 2).

In the model organism *S. cerevisiae*, nonselective autophagy and autophagosome formation is divided into induction, nucleation, expansion, fusion and breakdown phases (Rubinsztein et al. 2012) (Fig. 1).

Induction begins with the sensing of nutrient starvation by target of rapamycin (Tor) kinase. Upon starvation, Tor kinase is inactivated and does not phosphorylate Atg13. Unphosphorylated Atg13 has a high affinity for the Atg1 kinase, leading to complex formation with Atg1, Atg17, Atg29 and Atg31 and phosphorylation of Atg2 (Chen and Klionsky 2011; Tanida 2011) (Fig. 3a). Nucleation starts with the accumulation of Atg proteins at the perivacuolar phagophore assembly site (PAS) (Abeliovich et al. 2000; Suzuki et al. 2001) and is regulated by complex I consisting of Vps34, Vps15, Atg14 and Atg6, which phosphorylates phosphatidylinositol at the PAS. Formation of complex I leads to the recruitment of additional Atg proteins required for phagophore formation (Suzuki and Ohsumi 2007) (Fig. 3b). The membrane structures for autophagosomes are assumed to be recruited by the integral membrane protein Atg9 since localization experiments identified Atg9 at endosomes in nonstarvation conditions and at the PAS under starvation conditions. Membrane protein Atg9 binds to Atg18, which is localized to the PAS by association with Atg2. In this way, Atg9 delivers membrane structures to the expanding PAS (Tanida 2011) (Fig. 3b).

During phagophore expansion, a crescent-like structure sequesters cytoplasm and organelles into the double-membraned autophagosome (Klionsky et al. 2003). Two conjugation pathways similar to the ubiquitin conjugation pathway are crucial for autophagosome formation. A major structural component of autophagosomes is an Atg8-phosphatidylethanolamine (PE) conjugate. The formation of the Atg8-PE conjugate involves the protease Atg4, the E1-like enzyme Atg7 and the E2-like enzyme Atg3. In the second conjugation system, the ubiquitin-like protein Atg12 is covalently attached to Atg5 by the E1-like enzyme Atg7 and the E2-like enzyme Atg10 (Shintani et al. 1999; Tanida et al. 1999). The Atg12–Atg5–Atg16 protein complex localizes the Atg8–PE conjugate at the PAS (Fig. 3c) (Geng and Klionsky 2008). The autophagosome is delivered to the vacuole and during fusion, the outer autophagosomal membrane fuses with the vacuolar membrane, releasing a vesicle composed of the inner

Table 1 Mutant phenotypes of autophagy-related genes in filamentous ascomycetes

S. cerevisiae gene	Function	Filamentous ascomycete: species, orthologue[a]	Loss of function phenotype	Reference
TOR1/TOR2	Target of rapamycin, Ser/Thr protein kinase	*Fusarium fujikuroi*, *tor*	Essential for viability	(Teichert et al. 2006)
ATG1	Ser/Thr protein kinase	*Aspergillus fumigatus*, *Afatg1*	Abnormal conidiophore development and reduced conidiation, vegetative growth impaired under nitrogen, carbon and metal ion starvation conditions	(Richie et al. 2007)
		Aspergillus niger, *atg1*	Decreased conidiation, reduced vegetative growth, enhanced cell death of older thick hyphae during submerged growth	(Nitsche et al. 2013)
		Aspergillus oryzae, *Aoatg1*	Decreased conidiation and aerial hyphae formation	(Yanagisawa et al. 2013)
		Neurospora crassa, *apg-1*	Sensitive to menadione and peroxide, decreased growth in the presence of sorbitol and sodium chloride, defects in asexual and sexual growth and development	(Park et al. 2011)
		Magnaporthe oryzae, *Moatg1 M. grisea*, *MgATG1*	Nonpathogenic, fewer lipid droplets in conidia, lower turgor pressure of the appressorium, slower germination of conidia, required for macroautophagy of nuclei	(He et al. 2012; Kershaw and Talbot 2009; Liu et al. 2007)
		Metarhizium robertsii, *MrATG1*	Impairment of lipid droplet accumulation and virulence	(Duan et al. 2013)
		Penicillium chrysogenum, *atg1*	Reduction in conidiospore formation, impairment of autophagy, delay in cell degeneration, enhanced penicillin production	(Bartoszewska et al. 2011b)
		Podospora anserina, *PaATG1*	Slower growth rate, lower density of aerial hyphae, decreased pigmentation of the mycelium, no protoperithecia, female sterile	(Pinan-Lucarré et al. 2005)
ATG13	Phosphoprotein component of Atg1 complex	*A. oryzae*, *Aoatg13*	Number of conidia decreased	(Kikuma and Kitamoto 2011)
		M. oryzae, *Moatg13*	Reduced pathogenicity	(Dong et al. 2009; Kershaw and Talbot 2009)
ATG17	Scaffold potein responsible for pre-autophagosomal structure organization	*A. niger*, *atg17*	Little or no phenotypic effect	(Nitsche et al. 2013)
		M. oryzae, *Moatg17*	Nonpathogenic	(Kershaw and Talbot 2009)
ATG29	Protein specifically required for autophagy; may function in autophagosome formation at the pre-autophagosomal structure in collaboration with other autophagy proteins	*M. oryzae*, *Moatg29*	Able to cause rice blast disease and did not affect conidial or appressorial autophagy	(Kershaw and Talbot 2009)
Vesicle nucleation				
VPS34	Class III PtdIns 3 kinase of Vps34 complex	*Sordaria macrospora*, *Smvps34*	Essential for viability	(Voigt et al. in press)
VPS15	Ser/Thr protein kinase, component of Vps34 complex	*S. macrospora*, *Smvps15*	Essential for viability	(Voigt et al. in press)
ATG6	Component of Vps34 complex	*M. oryzae, Moatg6*	Nonpathogenic	(Kershaw and Talbot 2009)
Vesicle expansion				
ATG3	E2-like enzyme, conjugates PE to Atg8	*M. oryzae*, *Moatg3*	Nonpathogenic	(Kershaw and Talbot 2009)
ATG4	Cysteine protease cleaves C terminus of Atg8	*A. oryzae*, *Aoatg4*	No conidiospores	(Kikuma and Kitamoto 2011)
		M. oryzae, *Moatg4*	Nonpathogenic, reduction of aerial hyphae, conidiation, perithecia formation and delay of conidial germination and appressorium formation, required for macronucleophagy	(He et al. 2012; Kershaw and Talbot 2009; Liu et al. 2010)
		Metarhizium robertsii, *MrATG4*	Impairment of lipid droplet accumulation and virulence	(Duan et al. 2013)
		S. macrospora, *Smatg4*		(Voigt and Pöggeler 2013)

Table 1 (continued)

S. cerevisiae gene	Function	Filamentous ascomycete: species, orthologue[a]	Loss of function phenotype	Reference
			No fruiting-body development, impaired vegetative growth and ascospore germination	
ATG5	Conjugated to Atg12 through internal Lys, E3-like enzyme activity	*Beauveria bassiana, BbATG5*	Increased sensitivity to nutrient limitation, decreased germination and growth, reduced conidiation, modest decrease in virulence	(Zhang et al. 2013)
		M. oryzae, *Moatg5*	Nonpathogenic, shortened aerial hyphae, decreased conidiation and perithecia formation, delayed conidial germination and appressorium formation	(Kershaw and Talbot 2009; Lu et al. 2009)
		Trichoderma reesei, *TrATG5*	Sensitive to nutrient starvation, abnormal conidiophores and reduced production of conidia	(Liu et al. 2011)
ATG7	E1-like enzyme, activates Atg8 and Atg12	*M. oryzae*, *Moatg7*	Nonpathogenic	(Kershaw and Talbot 2009)
		S. macrospora, *Smatg7*	Essential for viability	(Nolting et al. 2009)
ATG8	Ubiquitin-like protein conjugated to PE	*A. niger*, *atg8*	Decreased conidiation, reduced vegetative growth, enhanced cell death of older thick hyphae during submerged growth	(Nitsche et al. 2013)
		A. oryzae, *Aoatg8*	Unable to form aerial hyphae and conidia, reduced germination of conidia	(Kikuma et al. 2006)
		Colletotrichum orbiculare, *CoATG8*	Nonpathogenic, nonfunctional appressoria, slightly reduced growth on nutrient-rich medium, severe reduction in conidiation	(Asakura et al. 2009)
		Fusarium graminearum, *Fgatg8*	No perithecia, reduced conidia production, reduced aerial mycelium and vegetative growth	(Josefsen et al. 2012)
		M. oryzae, *Moatg8*	Nonpathogenic, severe reduction in vegetative growth and conidiation	(Deng et al. 2009; Kershaw and Talbot 2009; Veneault-Fourrey et al. 2006)
		M. robertsii, *MrATG15*	No appressoria and impairment in defense response against insect immunity, impairment of lipid droplet accumulation and virulence	(Duan et al. 2013)
		P. anserina, *idi-7*	Induced during incompatibility reaction, lower density of aerial hyphae, decreased pigmentation of the mycelium, absence of femalereproductive structures	(Pinan-Lucarré et al. 2003)
		S. macrospora, *Smatg8*	No fruiting-body development, impaired vegetative growth and ascospore germination	(Voigt and Pöggeler 2013)
ATG10	E2-like enzyme, conjugates Atg5 and Atg12	*M. oryzae*, *Moatg10*	Nonpathogenic	(Kershaw and Talbot 2009)
ATG12	Ubiquitin-like protein conjugated to Atg5	*M. oryzae*, *Moatg12*	Nonpathogenic	Kershaw and Talbot 2009)
ATG16	Component of Atg5–Atg12 complex	*M. oryzae*, *Moatg16*	Nonpathogenic	(Kershaw and Talbot 2009)
Breakdown and recycling				
ATG2	Peripheral membrane protein, interacts with Atg9, vacuolar import	*M. oryzae*, *Moatg2*	Nonpathogenic, reduced conidiospore and appressoria formation	(Dong et al. 2009; Kershaw and Talbot 2009)
ATG9	Integral membrane protein, interacts with Atg2	*M. oryzae*, *Moatg9*	Nonpathogenic, reduced conidiospore and appressoria formation	(Dong et al. 2009; Kershaw and Talbot 2009)
ATG15	Lipase for vacuolar lysis of autophagic bodies	*A.oryzae Aoatg15*	No conidiation, autophagic bodies accumulated in vacuoles	(Kikuma and Kitamoto 2011)
		M. oryzae, *Moatg15*	Nonpathogenic	(Kershaw and Talbot 2009)
		M. robertsii, *MrATG15*	Impairment of lipid droplet accumulation and virulence	(Duan et al. 2013)
		F. graminearum, *Fgatg15*		(Nguyen et al. 2011)

Table 1 (continued)

S. cerevisiae gene	Function	Filamentous ascomycete: species, orthologue[a]	Loss of function phenotype	Reference
			Reduced vegetative growth, aerial hyphae conidia production, germination rate, aberrant conidia shapes, reduced in storage lipid degradation under starvation conditions	
ATG18	Peripheral membrane protein, PI(3,5)P binding	*M. oryzae*, *Moatg18*	Reduced pathogenicity, conidiospore and appressoria formation	(Dong et al. 2009; Kershaw and Talbot 2009)
Selective autophagy				
ATG11	Peripheral membrane protein required for delivery of aminopeptidase I (Lap4p) to the vacuole in the cytoplasm-to-vacuole targeting pathway; also required for pexophagy	*M. oryzae*, *Moatg11*	Little or no phenotypic effect	(Kershaw and Talbot 2009)
ATG24	Sorting nexin, involved in the retrieval of late-Golgi SNAREs from the post-Golgi endosome to the trans-Golgi network and in cytoplasm to vacuole transport	*M. oryzae*, *Moatg24*	Little or no phenotypic effect	(Kershaw and Talbot 2009)
ATG26[b]	Sterol glucosyltransferase involved in pexophagy	*C. orbiculare Coatg26*	Little or no phenotypic effect, host invasion impaired	(Asakura et al. 2009)
		M. oryzae, *Moatg26*	Little or no phenotypic effect	(Kershaw and Talbot 2009)
ATG27	Type II membrane protein that binds phosphatidylinositol 3-phosphate, required for the cytoplasm-to-vacuole argeting (Cvt) pathway	*M. oryzae*, *Moatg27*	Little or no phenotypic effect	(Kershaw and Talbot 2009)
ATG28[b]	Degradation of peroxisomes	*M. oryzae*, *Moatg28*	Little or no phenotypic effect	(Kershaw and Talbot 2009)

[a] Gene designation according to reference

[b] According to *Pichia pastoris*, not involved in autophagy in *S. cerevisiae*

17 core ATG proteins	
ATG1	**ATG10**
ATG2	**ATG12**
ATG3	**ATG13**
ATG4	**ATG14**
ATG5	**ATG15**
ATG6	**ATG16**
ATG7	**ATG18**
ATG8	**ATG22**
ATG9	

19 specific ATG proteins for induction and selective autophagy			
Autophagy induction	*Cvt Pathway*	*Pexophagy*	*Mitophagy*
ATG17	ATG19	ATG25	ATG32
ATG29	ATG21	**ATG26**	**ATG33**
ATG31	ATG23	**ATG28**	
	ATG27	ATG30	
	ATG34	**ATG35**	
		ATG36	
	ATG11, ATG20, **ATG24**		

Fig. 2 Conservation of *atg* genes in *Sordaria macrospora.* Thirty-six *atg* genes have been identified in yeasts (Inoue and Klionsky 2010; Motley et al. 2012; Nazarko et al. 2011; Suzuki et al. 2010). In *S. macrospora*, the 17 core *atg* genes and nine of the 19 genes involved in the induction of autophagy and selective autophagy are conserved when compared with the yeast homolog. *Bold and underlined*, proteins conserved in *S. macrospora* (*e* value, $<e^{-10}$); *bold*, proteins with similarity (*e* value, $>e^{-10}$); *grey*, no significant homolog in *S. macrospora*

membrane and the cytoplasmic contents. The remaining single-membraned vesicle within the vacuole is called an autophagic body. Breakdown of autophagic bodies is mediated by vacuolar hydrolases such as the lipase Atg15. Degradation products are released into cytoplasm via permeases such as Atg22 (Baba et al. 1995; Epple et al. 2001; Suriapranata et al. 2000) (Fig. 3d).

In addition to carbon starvation, autophagy in filamentous ascomycetes can be induced by the macrolide antibiotic rapamycin (Kikuma et al. 2006; Pinan-Lucarré et al. 2006). Both induction pathways are regulated by inactivation of the Tor kinase (Fig. 3). To determine if the two modes of induction have the same long-term impact on biotechnologically important *Aspergilli*, Kim et al. (2011) compared the proteomes of carbon-starved and rapamycin-treated *Aspergillus nidulans* cultures with nonstarved cultures. They identified 26 proteins with significantly different expression, including regulators for polar growth and utilization of alternative carbon sources. The majority of proteins is upregulated only in starvation conditions, and not in rapamycin-treated cultures and only three proteins share a profile in both conditions. These results suggest that carbon starvation triggers a more significant transcriptional response than growth in the presence of rapamycin (Kim et al. 2011).

Table 1 summarizes the autophagy genes that have been analyzed so far in filamentous ascomycetes. Autophagy-defective mutants are usually more susceptible to starvation and display defects in formation of aerial hyphae, conidiospores and protoperithecia, as well as in appressorium formation and in pathogenicity. The specific functions of autophagy in filamentous ascomycetes are described below. Methods useful for measuring the rate of autophagy induction in filamentous fungi have been described by Deng et al. (2008) and recently summarized by Klionsky et al. (2012).

Recycling of nutrients by organelle autophagy

Due to the specialized lifestyle of filamentous ascomycetes particular attention was paid to autophagy of organelles such as nuclei, peroxisomes and mitochondria (Shoji and Craven 2011). In contrast to unicellular yeasts that contain only a single nucleus per cell, filamentous fungi form an interconnected mycelium with many multinucleate hyphae. Filamentous ascomycetes may contain up to 100 nuclei in a single hyphal compartment and in many species the nuclei are able to move almost unimpeded through pores in cross walls (septa) (Roper et al. 2011). Another distinguishing feature of filamentous ascomycetes and ascomycetous yeasts is growth by tip extension. Extended hyphal tips are filled with cytoplasm and nuclei from subapical and basal hyphal compartments. Thus, a mycelium has young, actively growing hyphae at the colony margin surrounding an older, inner hyphal network that recycles nutrients to fuel the actively growing tips (Glass et al. 2004). Consequently, the cellular architecture of a hyphal compartment depends on its age and position in the mycelial colony. This applies especially to mitochondria and vacuoles. At hyphal tips, mitochondria appear as long, thin tubules whereas mitochondria in basal compartments are shorter (Bowman et al. 2009; Shoji et al. 2006b). Hickey and Read (2009) stained hyphae with rhodamine-123, a potentiometric dye, to show that mitochondria are most active in the growing tip.

Vacuoles are similarly pleiomorphic; they are small (1–3 μm) and spherical at the hyphal tips, tubular in subapical regions or in aerial hyphae that are not in contact with nutrients, and large ovoid–spherical organelles in basal hyphae that sometimes occupy the entire compartment volume (Bloemendal et al. 2010; Hickey and Read 2009; Shoji et al. 2006b). The connection between pleiomorphic vaculoar features in filamentous fungi and nutrient recycling by autophagy was first seen by Shoji et al. (2006a) who discussed the possible involvement of vacuoles in degradation, transport and nutrient recycling from old hyphae to the growing tip. Later, Shoji et al. (2010) used enhanced green fluorescent protein to label organelle markers in *A. oryzae* and showed that macroautophagy mediates degradation of basal hyphal organelles including peroxisomes, mitochondria and entire nuclei. They further showed that the absence of functional autophagy drastically reduces hyphal growth during nutrient depletion (Shoji et al. 2010). Recently, Gao et al. (2013) demonstrated that vacuole morphology and

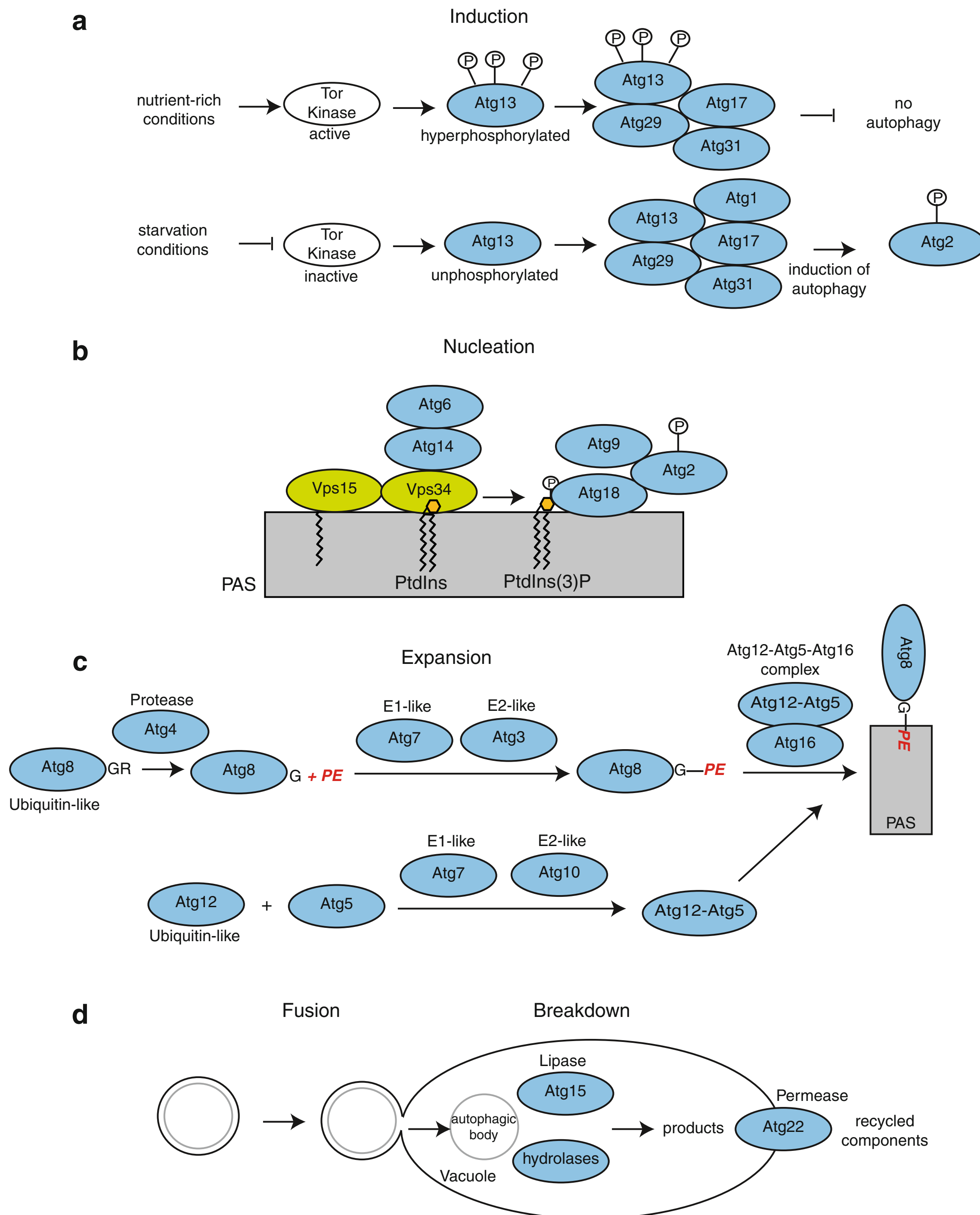

Fig. 3 Schematic illustration of the molecular mechanism of autophagy. **a** Induction of autophagy by sensing of nutrient limitation. **b** Nucleation mediated by phosphorylation of phosphatidylinositol at the PAS catalyzed by complex I. **c** Expansion of the phagophore by conjugation of Atg8-PE to PAS via the Atg8 and Atg12 conjugation pathways. **d** Fusion of the autophagosome with the vacuole and breakdown of the autophagic body within the vacuole by hydrolases. *PAS* phagophore assembly site, *PE* phosphatidylethanolamine, *PtdIns* phosphatidylinositol, *PtdIns(3)P* phosphatidylinositol-3-phosphate

vacuolar fusion events are essential for autophagy. Deleting the homolog of the *S. cerevisiae MON1* gene in *M. oryzae*, which is essential for vacuole morphology and vesicle fusion in yeast, results in vacuole and vesicle fusion defects. The *ΔMomon1* mutant has small punctuated vacuoles in hyphae and is blocked in autophagy.

In the unicellular yeast *S. cerevisiae*, the pinching-off of nonessential portions of the nucleus at nucleus–vacuole junctions and their release into the vacuole has been described as piecemeal microautophagy of the nucleus (PMN) (Kvam and Goldfarb 2007; Roberts et al. 2003). In contrast to *S. cerevisiae*, in *A. oryzae* only macroautophagy of whole nuclei occurs in basal hyphae and PMN has not been observed (Shoji et al. 2010). Nuclei are therefore proposed to function in storage locations for the growth-limiting nutrients phosphor and nitrogen (Maheshwari 2005; Shoji and Craven 2011). Peroxisomes and mitochondria are also preferentially degraded in the basal hyphae of filamentous ascomycetes (Shoji et al. 2010; Voigt and Pöggeler 2013). In yeast and mammals, two other types of selective organelle autophagy have been described: ribophagy, the specific degradation of ribosomes, and reticulophagy, the removal of portions of the ER (Cebollero et al. 2012; Suzuki 2013). Kimura et al. (2011) showed that late-phase cultures of *A. oryzae* deliver a majority of the ER in basal hyphae to vacuoles. They also demonstrated that misfolded secretory α-amylase AmyB accumulating in the ER is removed in an autophagy-dependent manner.

In *S. cerevisiae*, the ubiquitin proteinase Ubp3 and its cofactor Bre5 are involved in the selective degradation of ribosomes (Kraft et al. 2008). A ribophagy-like process has not yet been described in filamentous ascomycetes; however, filamentous ascomycetes have a homolog of Ubp3 (Voigt and Pöggeler, unpublished). Thus, ribophagy could also take place in old or nutrient-depleted hyphal compartments of filamentous ascomycetes.

Autophagy and pathogenicity

Evidence from the last 7 years shows that autophagy is not only important for filamentous growth under starvation and nonstarvation conditions but is often a prerequisite for pathogenicity as well (Table 1). Veneault-Fourrey et al. (2006) demonstrated that disruption of autophagy by deletion of the *atg8* gene rendered the rice blast fungus *M. oryzae (grisea)* nonpathogenic. In *M. oryzae*, germinating conidiospores differentiate an appressorium at the tip of the germ tubes that penetrates the outer cuticle of a rice leaf by generating an enormous turgor pressure. During appressorium maturation, the conidiospore delivers its content to the appressorium, then collapses and dies (Wilson and Talbot 2009). In the absence of an intact autophagy machinery, appressoria are formed but conidia stay intact and autophagy mutants are unable to penetrate plant leaves (Liu et al. 2007, 2010; Lu et al. 2009; Veneault-Fourrey et al. 2006). Systematic deletion of 22 conserved *atg* genes in *M. oryzae* revealed that the absence of any of the genes necessary for nonselective autophagy impairs pathogenicity, whereas the absence of genes necessary for selective autophagy are dispensable for appressorium-mediated plant infection (Kershaw and Talbot 2009) (Table 1). Transcriptional profiles of appressorium development using next-generation sequencing revealed that some genes encoding autophagy-related proteins are upregulated during early stages of appressorium formation (Soanes et al. 2012).

The collapse of the conidiospore during infection is accompanied by nuclear degeneration in the spore (Veneault-Fourrey et al. 2006). Recently, He et al. (2012) investigated whether the degradation of nuclei in spores requires PMN. They deleted *Movac8* and *Motsc13*, which encode homologs of conserved components of the *S. cerevisiae* PMN pathway. Analysis of the deletion mutants revealed that both MoVAC8 and MoTSC13 are dispensable for nuclear breakdown during plant infection, while components of the nonselective autophagy machinery such as ATG1 and ATG4 are required for infection-associated nuclear degeneration in *M. oryzae*. In addition to defects in nuclear degeneration during appressorium formation, deletion of *Moatg4* and *Moatg8* results in drastic reduction of asexual conidiospore formation and thus propagation of rice blast disease (Deng et al. 2009; Liu et al. 2010). However, not only nucleophagy is important for plant infection pexophagy seems to be required as well. The cucumber pathogen *Colletotrichum orbiculare* degrades peroxisomes via pexophagy during appressoria formation. A *ΔCoatg26* mutant develops appressoria but is defective in the subsequent host invasion step (Asakura et al. 2009; Bertoni 2009).

Interestingly, exogenous supply of glucose or sucrose can significantly suppress conidiation defects, but not appressorium penetration defects in an *M. oryzae* autophagy-deficient *Moatg8* deletion mutant (Deng et al. 2009). Mass spectrometry comparison of the Δ*Moatg8* proteome with a complemented mutant revealed that the mutant accumulates the cytosolic glycogen phosphorylase Gph1 and has a high steady state level of glycogen. Deletion of *GPH1* in the Δ*Moatg8* mutant restores the conidiation defect of the mutant. Furthermore, autophagy-dependent delivery of cytosolic glycogen into the vacuole and glycogen breakdown by the vacuolar glucoamylase Sga1 is crucial for conidiospore development in *M. oryzae* (Deng and Naqvi 2010). In addition to vacuolar glycogen breakdown, the autophagic degradation of lipids and proteins in the vacuole is equally important for the pathogenicity of plant pathogenic fungi. In *M. oryzae* and *Fusarium graminearum*, deletion of the gene encoding the homolog of the *S. cerevisiae* lipase Atg15 results in reduced degradation of storage lipids and severely attenuate infection of the host plant (Kershaw and Talbot 2009; Nguyen et al. 2011). An *M. oryzae* mutant carrying a deletion of the vacuolar protease gene *SPM1* revealed a retarded degradation of autophagic bodies and pleiotropic defects in conidiospore germination, appressorium formation, host invasion and postinvasive growth (Saitoh et al. 2009).

Similar to plant pathogens, deletion of autophagy-related genes in the entomopathogenic fungus *Metarhizium robertsii* affects host infection. However, in contrast to the plant pathogen *M. oryzae*, an ATG8-defective mutant of *M. robertsii* is unable to form appressoria and has an impaired defense against insect immunity. The mutant also displays a decreased accumulation of lipid droplets in conidiospores and reduced pathogenicity. Deletion of other conserved *M. robertsii atg* genes (*Mratg1*, *Mratg4*, and *Mratg15*) also affects lipid biogenesis and insect infection, but not appressorium formation (Table 1) (Duan et al. 2013). Contrary to these observations, the *BbATG5* gene of the entomopathogenic fungus *Beauveria bassiana* is not required for pathogenesis and *ΔBbATG5* mutants show only a modest decrease in virulence (Zhang et al. 2013). Similarly, investigations of autophagy in the human pathogen *Aspergillus fumigatus* revealed that despite having drastic effects on vegetative growth under nutrient-limited conditions, an autophagy-deficient *ΔAfatg1* mutant was fully virulent in a mouse model of invasive aspergillosis (Palmer et al. 2008; Richie et al. 2007). Interestingly, the decreased growth of the *ΔAfatg1* mutant under starvation conditions is restored by the addition of metal ions, suggesting a link between metal ion homeostasis and autophagy in *A. fumigatus* (Palmer et al. 2008; Richie and Askew 2008).

Autophagy affects secondary metabolite and heterologous protein production

Like many other microorganisms, filamentous ascomycetes can produce various secondary metabolites, not required for normal growth and development. These low molecular organic compounds include medically important compounds such as the pharmaceuticals penicillin, cephalosporin, cyclosporin or lovastatin, and poisonous mycotoxins such as aflatoxin and trichothecenes (Brakhage 2013; Keller et al. 2005). The biosynthesis of secondary metabolites usually occurs within different cellular compartments and peroxisomes are often involved (Bartoszewska et al. 2011a; Martín et al. 2012). In *Penicillium chrysogenum*, the biosynthesis of the β-lactam antibiotic penicillin starts within the cytosol and is continued in the peroxiomes (Meijer et al. 2010; Müller et al. 1992; Opaliński et al. 2010). A major pathway of peroxisome degradation is pexophagy. For this reason, Bartoszewska et al. (2011b) examined whether inhibition of autophagy is associated with increased penicillin production by deleting the *atg1* gene in *P. chrysogenum*. The *atg1* deletion mutants are impaired in autophagy and sporulation but significantly increase penicillin production. Using a structured kinetic model for growth, differentiation, and penicillin production in submerged *P. chrysogenum* fermentation, Paul and Thomas (1996) determined that penicillin production is related to the amount of the nongrowing hyphal subapical regions. Electron and fluorescent microscopy revealed that autophagy impairment delays autophagy-related disintegration in late subapical regions of hyphae and thereby enhances penicillin production (Bartoszewska et al. 2011b).

Among filamentous ascomycetes, the genus *Aspergillus* is an important fungal group used for large-scale production of enzymes, organic acids and heterologous proteins (Fleißner and Dersch 2010; Meyer et al. 2011; Punt et al. 2002; Schuster et al. 2002). Fungal strains often experience limited nutrients when cultivated in bioreactors because of poor mixing of viscous media or pellet formation (Kim et al. 2011). However, the role of autophagy in protein production under these conditions has only recently been examined. The analysis of genome-wide transcriptional changes caused by prolonged carbon starvation during submerged batch cultivation of *Aspergillus niger* revealed induction of autophagy-related genes. The analysis of genome-wide transcriptional changes caused by prolonged carbon starvation during submerged batch cultivation of *A. niger* revealed an induction of genes related to autophagy. Activation of autophagic processes under fermentation conditions is accompanied by intense remodeling and morphological changes. During starvation, carbon from endogenous resources is mobilized. Carbon starvation induces a transition from old (thick) hyphae to young (thin) hyphae. The secondary regrowth of thin nonbranching hyphae is fueled by endogenous carbon resources from old hyphae. Increased vacuolization in old compartments results in fragmentation and cell death and the emergence of empty hyphal compartments (Nitsche et al. 2012; Pollack et al. 2008). Deletion of *atg1* and *atg8* in *A. niger* accelerated the transition from thick to thin hyphae in autophagy-deficient mutants, suggesting that autophagy protects old hyphae from cell death under carbon-starvation conditions in submerged cultures (Nitsche et al. 2013). Fluorescence microscopy demonstrated that mitophagy is severely blocked in autophagy-deficient *Δatg1* and *Δatg8* *A. niger* mutants (Nitsche et al. 2013).

Protein degradation during the expression of heterologous proteins often results in low yields of the desired target protein. Recently, Yoon et al. (2013) demonstrated that autophagy is a bottleneck for heterologous protein production in *A. oryzae*. Heterologous expression of bovine chymosin in *Aoatg1*, *Aoatg13*, *Aoatg4*, *Aoatg8* and *Aoatg15* deletion mutants shows an up to 3-fold increase of production levels of chymosin compared to the control strain. However, the *A. oryzae* mutant strains also significantly decrease production of condiospores (see Table 1), which are required for inoculation of large-scale cultures. To overcome this problem, Yoon et al. (2013) constructed *Aoatg*-conditional strains in which the endogenous promoter was replaced with a thiamine-repressible promoter. Without thiamine, conidiation is enhanced, while thiamine repressed autophagy. Similar to the *Aoatg* deletion strains, chymosin production is significantly induced in the conditional strains.

Conclusion and outlook

This review shows that we are only beginning to understand how autophagy contributes to the growth and development of filamentous ascomycetes. Filamentous ascomycetes have a specific growth mode of apical tip extension and autophagy seems to be important for morphology even under nonstarvation conditions. Manipulation of autophagy offers the possibility of controlling and improving the production of secondary metabolites and heterologous proteins. Knowledge from future studies will define the characteristics of fungal autophagy and could help elucidate the relationship between autophagy and infection process by pathogenic fungi. Specifically modulating or blocking fungal autophagy could enable the identification of new targets for antifungal agents.

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