微生物学报
Acta Microbiologica Sinica
2019, 59(2): 224–234
http://journals.im.ac.cn/actamicrocn
DOI: 10.13343/j.cnki.wsxb.20180179

Review 综 述

Role of autophagy in the reproduction of pathogenic fungi

Chengli Fan[1], Anni Chang[2], Tongbao Liu[2*]

[1] College of Animal Science and Technology, Southwest University, Chongqing 400715, China
[2] State Key Laboratory of Silkworm Genomic Biology, Southwest University, Chongqing 400715, China

Abstract: Autophagy (macroautophagy) is an essential and highly conserved protein degradation mechanism in eukaryotes. In this process, cytoplasmic organelles, old proteins and other macromolecules are sequestered into a double membrane vesicle called autophagosome and delivered to a degradative organelle for degradation and recycling. Extensive studies have revealed that autophagy plays an essential role in the cellular processes such as cell differentiation, nutrient homeostasis and pathogenicity in pathogenic fungi. In this review, we introduce the process of autophagy and describe the role of autophagy in regulation of the fungal sexual reproduction, using the human fungal pathogen *Cryptococcus neoformans* as an example. Furthermore, we summarize the autophagy related genes studied so far and the deduced physiological functions of autophagy for proper asexual and/or sexual reproduction in model pathogenic fungi. We also discuss perspectives on autophagy function in fungal reproduction.

Keywords: autophagy, pathogenic fungi, fungal reproduction, mating, conidiation

Autophagy is an evolutionally conserved self-eating process in which cellular components such as organelles, aggregated proteins, invading microorganisms, and other cytoplasmic material are sequestered by a double-membrane structure called autophagosome and delivered to the degradative organelle for breakdown and recycling[1]. So far there are at least 42 autophagy-related genes (*ATG*s) have been identified in the model yeast *Saccharomyces cerevisiae* by genetic screening and many of them are conserve in fungi, plants and mammals[2]. There are three well-defined autophagy processes: macroautophagy, microautophagy and chaperone mediated autophagy[1,3–4]. Macroautophagy is the main pathway that involves delivery of cytosolic components to the vacuole/lysosome for degradation by double membrane vesicles known as autophagosome. Microautophagy, on the other hand involves direct engulfment of cytosolic material into the vacuole/lysosome. Chaperone mediated autophagy (CMA) is a complex and specific pathway for proteolysis of specific cytosolic proteins with the aid of chaperone molecules. Macroautophagy (referred to hereafter as autophagy) plays important roles to protect organism against diverse pathologies including infections, cancer, neurodegeneration, aging, and heart diseases[5]. Autophagy also appears to play a critical role in fungi, impacting growth,

Supported by the National Natural Science Foundation of China (31400133), by the Chongqing Research Program of Basic Research and Frontier Technology (cstc2017jcyjBX0034) and by the Fundamental Research Funds for the Central Universities (XDJK2016C097, XDJK2017D188)
*Corresponding author. Tel: +86-23-68251088; Fax: +86-23-68251128; E-mail: tongbaoliu@swu.edu.cn
Received: 23 April 2018; Revised: 15 July 2018; Published online: 24 July 2018

morphology, pathogenicity and development[6].

Pathogenic fungi include fungal species that can cause disease in plants, animals and human and have a great impact on agriculture and health care. Most pathogenic fungi undergo a life cycle composed of two important stages: asexual/sexual reproduction and invasive growth in the host tissues. Molecular mechanisms of autophagy have been extensively studied in many model pathogenic fungi such as *Magnaporthe oryzae* and *Fusarium graminearum* (Table 1). A number of reviews have summarized the role of autophagy in fungal development and pathogenicity[7–8]. In this review, we focus on the recent advances in our understanding of autophagy in fungal asexual and sexual reproduction.

1 The process of autophagy

Autophagy is a highly conserved cellular degradation process in which the cytoplasmic components can be sequestered by a double-membraned organelle called autophagosome and are subsequently transferred to vacuole or lysosome for cytoplasmic contents degradation and recycling[1]. Through this basic mechanism, autophagy plays a crucial role in cellular homeostasis as dysregulation of autophagy is associated with a wide range of

Table 1. Summary of autophagy functions in asexual and/or sexual reproduction in model pathogenic fungi

Fungus	Hosts	Modes of reproduction	Autophagy related genes involved	Asexual reproduction defects	Sexual reproduction defects	Deduced autophagy function	References
Aspergillus fumigatus	Human	Asexual/sexual	*ATG1*	Reduced conidiation	N.A.	Nitrogen metabolism	[23–24]
Beauveria bassiana	Insects	Asexual/sexual	*ATG1*, *ATG5*, *ATG8*, *VLP4*	Reduced conidiation and blastospore formation	N.A.	Not clear	[25–27]
Botrytis cinerea	Grape	Asexual/sexual	*ATG1*	Reduced conidiation and sclerotial formation	N.A.	Not clear	[28]
Cryptococcus neoformans	Human	Asexual/sexual	*ATG7*, *VPS34*, *ATG5*, *ATG8*, *ATG12*	N.A.	No basidiospore formation (*ATG5*, *ATG8*, *ATG12*)	Nuclear division	[29–31]
Colletotrichum orbiculare	Bean	Asexual/sexual	*ATG8*, *ATG26*	Reduced conidiation	N.A.	Not clear	[32–33]
Fusarium graminearum	Wheat/barley	Asexual/sexual	*ATG1*, *ATG5*, *ATG8*, *ATG9*, *ATG13–16*, *ATG20*, *ATG24*	Reduced conidiation	Reduced perithecia formation (*ATG1*, *ATG5*)	Lipid degradation	[34–37]
Fusarium oxysporum	Plant/human	Asexual	*ATG8*	Reduced conidiation	N.A.	Nuclear distribution	[38–39]
Magnaporthe oryzae	Rice/barley	Asexual/sexual	*ATG1*, *ATG4*, *ATG5*, *ATG8*, *ATG24*	Reduced conidiation	Reduced perithecia formation (*ATG4*, *ATG5*)	Lipid droplet degradation; nuclear degradation; glycogen breakdown	[17–21]
Metarhizium robertsii	Insects	Asexual	*ATG8*	Reduced conidiation	N.A.	Possibly lipid droplet degradation	[40]
Ustilago maydis	Maize	Asexual/sexual	*ATG1*, *ATG8*	Reduced teliospores production	N.A.	Possibly glycogen metabolism	[41–42]

The genes inside the parentheses were further analyzed and proved to be essential for fungal sexual reproduction in pathogenic fungi. N.A.: Not analyzed.

diseases such as neurodegeneration, cancer, myopathies, and diabetes and so on[9]. Autophagy can be triggered by various types of stress including starvation, hypoxia and hormonal stimuli[9]. Autophagy pathways can be broken down into the following five sequential steps: Induction and autophagosome nucleation, autophagosome expansion and completion, autophagosome fusion with the vacuole/lysosome, and cargo breakdown and recycling (Figure 1).

Fungal autophagy is typically induced by nutrient (e.g. carbon, nitrogen) starvation or in response to treatment with rapamycin. Under autophagy-inducing conditions, a membranous cistern called the phagophore begins to form. The phagophore is generated from the phagophore assembly site (PAS) that is a putative early autophagosome precursor. The second step of autophagy is autophagosome expansion. In this step, acquisition of extra lipids permits the expansion of the phagophore and subsequent engulfment of the cytoplasmic content for degradation. After that the inner and outer bilayer of the autophagosome fuses to form two distinct membranes, forming the complete double-layered autophagosome. The autophagosome then docks with the surface of a vacuole and its outer membrane fuses with the vacuole (in yeast or plants) or lysosome (in mammals) membrane to form autolysome. Hydrolytic enzymes from the vacuole or lysosome degrade the inner membrane of the autophagosome, gaining access to the cargo of the inner vesicle. In the last step, all the contents of the autophagosome are degraded, yielding basic metabolites that are transported into the cytoplasm to be reused as a source of energy or building blocks for new proteins and lipids[10].

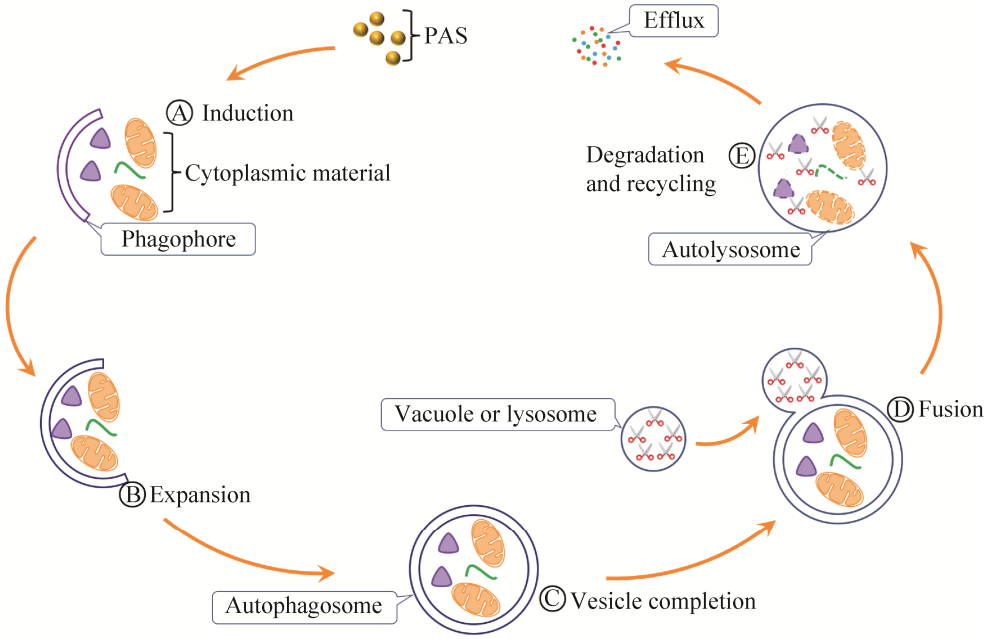

Figure 1. The model of autophagy in yeast cells. Autophagy pathway can be broken down into the following five steps: InductionⒶ and autophagosome nucleationⒷ, autophagosome expansion and completionⒸ, autophagosome fusion with the vacuole/lysosomeⒹ, cargo breakdown and recyclingⒺ. Autophagy is induced by an extracellular signal such as nutrient starvation. Membrane nucleate at the pre-autophagosomal structure (PAS) and a double membrane vesicle sequesters cytoplasmic cargo to form an autophagosome. The autophagosome subsequently docks with a vacuole and its outer membrane fuses with vacuolar membrane to form autolysosome, and the internal material is degraded. The resulting metabolites can then be recycled back to the cytoplasm for further use. The nomenclature for various autophagic structures is indicated.

2 Fungal asexual and sexual reproduction

Fungi produce spores, which may be asexual or sexual. The asexual spores are produced by mitosis having the genetic material inside, which allows them to make a whole new organism identical to its parent. Sexual reproduction enables genetic exchange in fungi and accelerates adaptation to a new environment. Fungal sexual reproduction is a complicated process dominated by two mating types. The process of fungal sexual reproduction involves mate recognition, cell-cell fusion yielding a zygote, generation of gametes via meiosis, and ploidy changes. Sexual reproduction has been studied to occur more predominantly in the Ascomycota and Basidiomycota phyla. There are two main types of sexual reproductions in fungi: homothallism, when mating occurs within a single individual, or in other words each individual is self-fertile; and heterothallism, when hyphae from a single individual is self-sterile and needs to interact with another compatible individual for mating to take place. Here we discuss fungal sexual reproduction using *C. neoformans* as an example.

C. neoformans is a basidiomycete yeast that can cause fungal meningoencephalitis in mostly immunocompromised individuals. As a heterothallic basidiomycete, *C. neoformans* has two mating type, α and **a**. Although *C. neoformans* is most commonly isolated as a budding yeast from patients and the environment, it can undergo a dimorphic transition to a filamentous growth form by two distinct differentiation pathways: mating (heterothallism) and monokaryotic fruiting (homothalism) (Figure 2). After fusion of haploid cells of α and **a** opposite mating types, dikaryotic filaments are produced and a basidia eventually formed in *C. neoformans.* Following the completion of meiosis finished inside a basidium, four chains of readily aerosolized basidiospores are produced on top of the basidium. Under laboratory conditions, *C. neoformans* var. *neoformans* strains can also differentiate and undergo monokaryotic fruiting to produce filaments and basidiospores[11]. Although monokaryotic fruiting was originally thought to be strictly haploid, mitotic and asexual, fruiting has recently been recognized to be a modified form of sexual reproduction occurring between strains of the same mating type[12] (Figure 2). Although mating and monokaryotic fruiting have similar morphological features, the hyphal cells that are produced during fruiting are mononucleate with unfused clamp connections, whereas those produced during mating contain two nuclei and are linked by fused clamp connections[11] (Figure 2).

In *C. neoformans*, sexual reproduction contributes to fungal virulence via the production of infectious spores, in that α isolates can be more virulent than congenic **a** isolates[13]. Spores and desiccated yeast cells are thought to be the initial infectious propagules to cause infection by *Cryptococcus* because they are small enough to fit down into the deep alveoli of the lung[14]. Spores are also documented to be infectious propagules in a serious of studies via inhalation and direct intracerebral infection[15].

Sexual reproduction enables the pathogenic fungi to proliferate and undergo genetic exchange in response to new environmental conditions such as stressful conditions, different host organisms, or changes in the host such as antimicrobial therapy. Further research of the sexual nature of pathogenic fungi will help to elucidate how fungi have evolved into successful pathogens.

3 Autophagy in fungal reproduction of model pathogenic fungi

Autophagy has important roles in various cellular functions including sporulation in various fungi. Natural induction of autophagy was reported in fungal asexual or sexual sporulation in numerous model pathogenic fungi. During fungal reproduction,

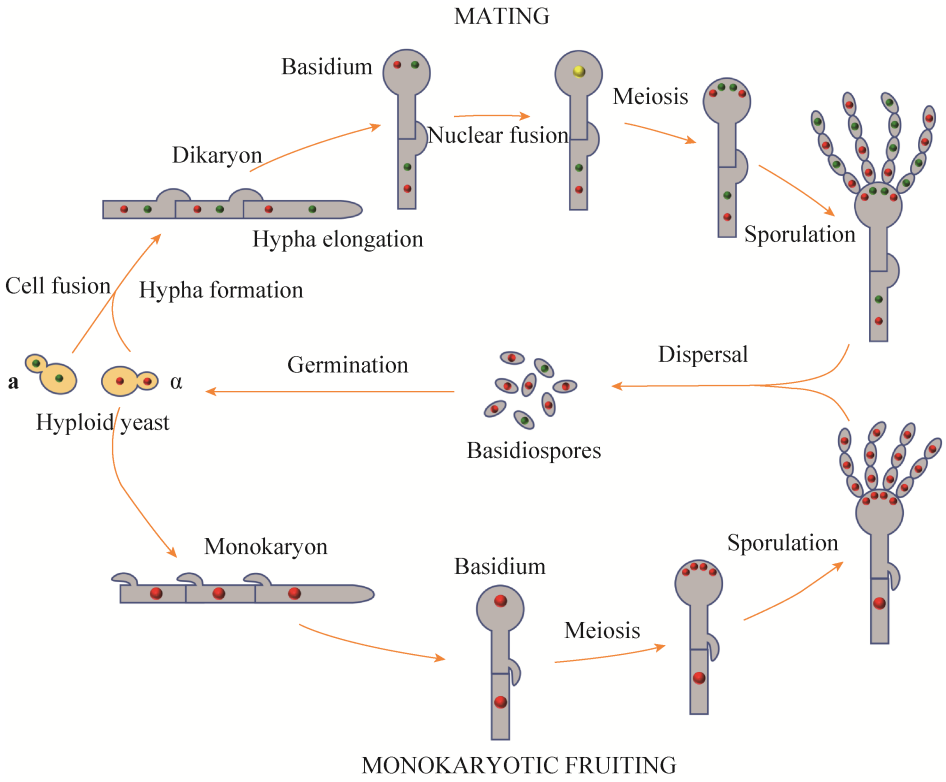

Figure 2. Model of sexual reproduction in *C. neoformans*. Under induction of nutrient-limiting conditions, α and **a** Cryprococcal yeast cells secrete peptide pheromones and trigger cell-cell fusion. The resulting dikaryotic cell initiates filamentous growth with two parental nuclei migrating coordinately in the hyphae. A septum then forms to separate two cells, one nucleus is transferred to the penultimate hyphal cell via a clamp connection, and the clamp cell fuse with hyphal cell. At the stage of basidium development, the two nuclei fuse and undergo meiosis to produce four meiotic nuclei that undergo mitosis to form four chains of basidiospores from the surface of the basidium. During monokaryotic fruiting, two cells of the same mating type, e.g., α cells, fuse to become diploid α/α cells either by endoduplication or by nuclear fusion. The diploid monokaryotic hyphae forms rudimentary clamp connections that are not fused to the preceding cell. At the stage of basidium development, meiosis occurs and four chains of haploid basidiospores are produced (modified from Lin and Heitman[11]).

autophagy may help to provide materials or energy source to build up new intracellular structures by breaking down of cellular components. This is particularly important because nutrient scarcity may commonly occur during fungal morphogenesis and development.

So far there are at least 42 autophagy-related genes (*ATG*s) have been identified in the model yeast *S. cerevisiae* by genetic screening and many of them are conserve in fungi, plants and mammals. In model filamentous fungi, *ATG1*, *2*, *4*, *5*, *7*, *8*, *9*, *15*, *17*, *18* and the phosphatidylinositol 3-kinase encoding gene *VPS34* are conserved with their orthologs in yeasts or animals[16]. Functional requirement of autophagy for fungal asexual or sexual development was confirmed by characterization of autophagy-deficient mutants in diverse model fungi as removing one of the conserved *ATG*s resulted in defects in asexual and/or sexual sporulation. In the next couple of sections, we will discuss the role and mechanism of autophagy in fungal reproduction of pathogenic fungi causing

diseases in plants, insects and human.

3.1 Autophagy regulates nutrient metabolism for fungal reproduction

During fungal development and morphogenesis, nutrient deprivation may commonly occur and autophagic degradation may need to produce abundant nutrients and small molecules for energy source or materials for building up new intracellular structures. Functional requirement of autophagy for fungal reproduction was investigated by characterization of autophagy-deficient mutants in diverse fungal systems in which autophagy-deficient fungal mutants showed defects in conidiation and/or sporulation. Studies on model pathogenic fungi such as *M. oryzae* have shown that autophagic degradation helps to utilize the cellular carbohydrate and nitrogen storages as a source of nutrients for fungal reproduction.

M. oryzae, also known as rice blast fungus, is a plant-pathogenic fungus that causes devastating blast disease in rice, wheat and barley. The asexual spores called conidia produced by *M. oryzae* are responsible for the spread of blast disease. Involvement of autophagy in conidiation in *M. oryzae* was relatively well studied and there are at least 5 *ATG* genes (*ATG1*, *ATG4*, *ATG5*, *ATG8*, *ATG14*) are confirmed to be essential for conidiation[17–21]. Among them, *ATG4* and *ATG5* were further confirmed to be necessary for perithecia formation in *M. oryzae*[18–21]. Conidiation defects in autophagy deficient strains could be restored by addition of carbon sources such as glucose or sucrose in *M. oryzae*[17]. A comparative proteomics study showed that glycogen phosphorylase was differentially expressed in the *atg8*Δ mutant, and further detailed analysis on glycogen catabolism indicated that autophagy-assisted glycogen homeostasis is important for *M. oryzae* conidiation[17–22]. These results suggest that autophagy plays an important role in carbon source utilization during *M. oryzae* conidiation.

Besides *M. oryzae*, autophagy assisted carbon utilization was also reported in *F. graminearum, M. robertsii* and *U. maydis*. So far, 10 autophagy-related genes, *ATG1*, *ATG5*, *ATG8*, *ATG9*, *ATG13–16*, *ATG20* and *ATG24*[34–36], were analyzed and shown to be essential for fungal asexual reproduction in *F. graminearum*. Among them, *ATG1* and *ATG5* were also found to be necessary for sexual reproduction in *F. graminearum* as deletion either *ATG1* or *ATG5* resulted in reduced Perithecia formation[35]. Functional analysis showed that the *FgATG15* disruptants were reduced in storage lipid degradation under starvation conditions, implicating autophagy's involvement in lipid turnover in *F. graminearum*[36]. Involvement of autophagy in lipid metabolism was also found in the entomopathogen *M. robertsii*. *M. robertsii* autophagy-deficient mutant *Mratg8*Δ in which *MrATG8*, an ortholog of yeast *ATG8*, was deleted failed to produce conidia either on a nutrient-poor minimum medium or a nutrient-rich potato dextrose agar, indicating autophagy is indispensable for *M. robertsii* to form conidiophores[40]. TEM analysis also found that the accumulation of lipid droplets in conidia was also significantly impaired in *Mratg8*Δ, indicating that autophagy is liked with lipid metabolism in *M. robertsii*. The role of autophagy in the development and virulence of *U. maydis*, a basidiomycetous fungus that causes smut on maize, was investigated using a reverse genetic approach. Deletion of the *ATG8* orthologue in *U. maydis* resulted in the formation of very few teliospores[42]. The reduced conidiation or teliospores formation of the *atg8* mutant in *F. graminearum*[36] and *U. maydis*[42] could potentially be explained by a lack of autophagic activity, which leads to a defect in glycogen metabolism.

Autophagy was also suggested to play role in recycling nitrogen sources as nutrient source. In *A. fumigatus*, one of the most common *Aspergillus* species causing disease in immunocompromised individuals, an autophagy-deficient strain of *A.*

fumigatus constructed by disrupting the *Afatg1* gene failed to produce conidia normally unless the nitrogen content of the medium was increased, suggesting that starvation-associated conidiation relies upon autophagy to provide sufficient nitrogen to support conidiophore development[24].

Hence, based on the functions of autophagy for nutrient catabolism in fungal reproduction of the model pathogenic fungi discussed above, we can appreciate that autophagy-assisted nutrient catabolism plays an essential role in fungal differentiation and development, including fungal asexual and sexual reproduction.

3.2 Autophagy contributes to nuclear degradation and/or distribution for fungal reproduction

Fungi produce asexual or sexual spores during the process of fungal reproduction. This process involves a series of nuclear events such as nuclear replication, migration, fusion, division and even the degradation of nuclei. Over the past decades, there are a large number of reports on the requirement of autophagy in fungal differentiation. However, the actual regulatory mechanism of autophagy in fungal reproduction remains largely unknown. Recently, autophagy-deficient mutants in *A. oryzae* showed defects in aerial hyphae development and asexual sporulation[43–46], indicating that autophagy is essential for fungal asexual reproduction in *A. oryzae*. The deduced function of autophagy involved in fungal asexual reproduction in *A. oryzae* might be related to the nuclei degradation mediated by autophagy[45–47].

Autophagy was also found to mediate nuclear degradation after hyphal fusion in the plant and human pathogen *F. oxysporum*. The *Foatg8*Δ strain in which the *F. oxysporum ATG8* gene was deleted displayed reduced rates of conidiation and were significantly attenuated in virulence on tomato plants and in the nonvertebrate animal host *Galleria mellonella*. The hyphae of the *Foatg8*Δ mutants contained a significant fraction of hyphal compartments with two or more nuclei while wild-type hyphae are almost exclusively composed of uninucleated hyphal compartments. Timelapse microscopy analyses revealed abnormal mitotic patterns during vegetative growth in the *Foatg8*Δ mutants, suggesting that autophagy mediates nuclear degradation after hyphal fusion and has a general function in the control of nuclear distribution in *F. oxysporum*[38].

C. neoformans is an encapsulated yeast-like fungal pathogen causing cryptococcal pneumonia or meningitis predominantly in immunocompromised individuals. Autophagy is required for successful infection in *C. neoformans*. The upstream inducer of autophagy Vps34 was proved to be essential for pathogenesis in *C. neoformans* because the *vps34*Δ mutant in which autophagy pathway was blocked showed reduced viability under starvation and fast clearance from the infected host tissue[29]. Similar results were obtained from the autophagy-deficient strain Cn*ATG8* RNAi strain and the *atg7*Δ mutants strain[29–31]. The above results of study showed that autophagy plays an important role in adapting to nutrient starvation conditions and fungal virulence in *C. neoformans*. However, the influence of autophagy on *Cryptococcus* mating or sexual reproduction has not yet been studied. Recently we examined three ubiquitin-like autophagy proteins, Atg5, Atg8 and Atg12, and the results showed that basidiospore production was completely blocked even though the autophagy-deficient mutants (*atg5*Δ, *atg5*Δ, and *atg12*Δ) can still form dikaryotic hyphae and basidia in the bilateral mating assay. Further study showed that the two haploid nuclei inside the dikaryotic hyphae cell can fuse but failed to separate resulting block of basidiospore formation at the stage of basidium development, indicating autophagy regulates meiosis and basidiospore formation in *C. neoformans* (data not published). Functions of autophagy in fungal reproduction in human fungal pathogens were also summarized in Table 1. Taken together, autophagy plays an important role in

autophagic degradation or distribution of the nuclei in fungal pathogens, which may physiologically contribute to the asexual and/or sexual reproduction in pathogenic fungi.

3.3 Autophagy in other fungal pathogens

Autophagy was also found to be essential for fungal reproduction in other model fungal pathogens as autophagy-deficient mutants showed defects in conidiation and/or sporulation in these fungi. Examples include: *B. cinerea Bcatg1*Δ[28], *B. bassiana Bbatg1*Δ[26], *Bbatg5*Δ[27], *Bbatg8*Δ[26], and *C. orbiculare atg8*Δ and *atg26*Δ mutants[32–33]. Similarly, The autophagy-related gene *TrATG5*, a homolog of *S. cerevisiae ATG5*, was found to be essential for autophagy, conidiophore formation and asexual sporulation in *T. reesei*[48]. However, the mechanistic role of autophagy in fungal reproduction remains unknown and further mechanistic studies are needed to determine how autophagy regulates the reproduction in these fungi.

4 Conclusions

In the past two decades, functions of autophagy have been extensively studied in various model fungi and much progress has been made in our understanding of the disease mechanisms of pathogenicity of fungal pathogens. However, our knowledge about specific functions of autophagy in fungal development especially in fungal sexual and asexual reproduction remains limited. Current and relevant studies focused mainly on the phenotypic analysis of the autophagy-deficient mutants and there has been very little research on how autophagy regulates fungal reproduction. During fungal growth, development and reproduction, autophagy helps the fungi to transport the nutrients to the new cells by regulating the utilization of their own cellular nutrient storage. Thus, the deeper and more extensive researches are needed to further enrich our knowledge on the regulation of autophagy during fungal development and reproduction.

In addition, fungal development often linked to pathogenicity of pathogenic fungi as most of the autophagy-deficient mutants having developmental defects reduce or lose pathogenicity in pathogenic fungi. During the infection of a pathogen, autophagy helps the fungus to adapt to the adverse conditions and better infect and colonize the host. Considering the importance of pathogenic fungi in health care and agricultural production, key autophagy-related proteins need to be taken into consideration as potential antifungal targets for pharmaceutical development. Therefore, further studies on the roles of autophagy in fungal development and pathogenesis are warranted, and may aid to the future development of new fungicides and control measures of fungal diseases in plants and humans.

Acknowledgments

We thank Dr. Chaoyang Xue at Rutgers University for critical reading of the manuscript and valuable comments for the study.

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自噬在病原真菌生殖中的作用

范成莉[1]，常安妮[2]，刘同宝[2*]

[1]西南大学动物科技学院，重庆 400715

[2]西南大学家蚕基因组生物学国家重点实验室，重庆 400715

摘要：自噬是真核生物中重要且高度保守的蛋白降解过程。在此过程中，细胞中的细胞器、长寿蛋白及其他大分子物质被双层膜的自噬体包裹并运送至降解细胞器中进行降解并重新利用。自噬在病原真菌诸如细胞分化、营养动态平衡以及致病性等各种细胞过程中起重要作用。在本综述中，我们简要介绍了自噬过程，并以人体病原真菌新生隐球菌为例介绍了病原真菌的有性生殖过程；同时我们也总结了目前模式病原真菌中自噬相关基因的研究情况以及自噬调控病原真菌无性和有性生殖的可能机理；最后我们总结全文并讨论了未来自噬调控真菌有性生殖机理研究的工作方向。

关键词：自噬，病原真菌，真菌生殖，交配，产孢

(本文责编：李磊)

基金项目：国家自然科学基金(31400133)；重庆市基础科学与前沿技术研究重点项目(cstc2017jcyjBX0034)；中央高校基本业务费(XDJK2016C097，XDJK2017D188)

[*]**通信作者**。Tel：+86-23-68251088；Fax：+86-23-68251128；E-mail：tongbaoliu@swu.edu.cn

收稿日期：2018-04-23；**修回日期：**2018-07-15；**网络出版日期：**2018-07-24