Uth1p Is Involved in the Autophagic Degradation of Mitochondria*

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Ingrid Kíssová, Maïka Dedefieu, Stéphane Manon, and Nadine Camougrand§

From the Unité Mixte de Recherche 5095 CNRS, Université de Bordeaux 2, 33077 Bordeaux, France

The absence of the outer mitochondrial membrane protein Uth1p was found to induce resistance to rapamycin treatment and starvation, two conditions that induce the autophagic process. Biochemical studies showed the onset of a fully active autophagic activity both in wild-type and Δuth1 strains. On the other hand, the disorganization of the mitochondrial network induced by rapamycin treatment or 15 h of nitrogen starvation was followed in cells expressing mitochondria-targeted green fluorescent protein; a rapid colocalization of green fluorescent protein fluorescence with vacuole-selective FM4-64 labeling was observed in the wild-type but not in the Δuth1 strain. Degradation of mitochondrial proteins, followed by Western blot analysis, did not occur in mutant strains carrying null mutations of the vacuolar protease Pep4p, the autophagy-specific protein Atg5p, and Uth1p. These data show that, although the autophagic machinery was fully functional in the absence of Uth1p, this protein is involved in the autophagic degradation of mitochondria.

The major cellular degradation pathways involved in protein and organelle turnover are autophagy and proteasome-mediated proteolysis. These processes are important for maintaining a controlled balance between anabolism and catabolism in order to have normal cell growth and development. These degradation pathways permit the cell to eliminate unwanted or unnecessary organelles and recycle the components for reuse. In eukaryotic cells, the lysosomes or the vacuole are major degradative organelles that contain a range of hydrolases able to degrade all the cellular constituents. During the last decade, autophagy has emerged as a crucial membrane trafficking process that transports bulk cytoplasm and sometimes entire organelles to the lysosome/vacuole for recycling in response to nutrient starvation or under specific physiological conditions (see Refs. 1 and 2 for reviews). Autophagy has two major forms, microautophagy and macroautophagy. Microautophagy operates by protruding or invaginating a portion of the vacuolar membrane to engulf cytosol or organelles. Only limited knowledge is available about microautophagy, which has been best characterized for the degradation of peroxisomes (3, 4) and selective portions of the nucleus (5). Macroautophagy, of which the molecular aspects are better characterized, involves the non-selective sequestration of large portions of the cytoplasm into double membrane structures termed autophagosomes and their delivery to the vacuole for degradation.

Although the normal function of autophagy is thought to provide amino acids to starved cells, a fair amount of evidence suggests that it could also be required for the elimination of selected organelles, namely mitochondria, under peculiar conditions. In mammalian cells, autophagic removal of mitochondria has been shown to be triggered following a process of induction/blockade of apoptosis (6, 7). Also, regulation of apoptosis and autophagy by the Akt/protein kinase B-signaling pathway has been evidenced (8, 9). Finally, molecular data suggest that autophagy-specific proteins might also be involved in the regulation of apoptosis (10). Because mitochondrial events are now regarded as a crucial step in apoptosis, this idea indicates that damaged mitochondria (following apoptotic induction) could control their own degradation by an autophagic process (11). This possibility is also supported by the observation that the overexpression of anti-apoptotic proteins, such as Bcl-2, is able to block autophagy (12) and that down-regulation of Bcl-2 induces autophagy (13). Also, the opening of the mitochondrial permeability transition pore, often considered to be a crucial event regulating the initial steps of apoptosis, induces the colocalization of mitochondrial and lysosomal markers, which is typical of an autophagic process in mammalian cells (14).

In yeast, a study reported the presence of mitochondria in autophagosomes following autophagy induction by nitrogen starvation (15). Under natural conditions, yeast often faces environmental changes requiring a modulation of its mitochondrial content (reviewed in Refs. 16, 17, and 18). For example, the shift from a respiratory carbon source to a fermentative carbon source or, more drastically, the shift from aerobic to anaerobic conditions is accompanied by a decrease of both the amount and the enzymatic equipment of mitochondria. Clearly, the possibility is also supported by the observation that the overexpression of anti-apoptotic proteins, such as Bcl-2, is able to block autophagy (12) and that down-regulation of Bcl-2 induces autophagy (13). Also, the opening of the mitochondrial permeability transition pore, often considered to be a crucial event regulating the initial steps of apoptosis, induces the colocalization of mitochondrial and lysosomal markers, which is typical of an autophagic process in mammalian cells (14).

In the present study, we used the autophagy-inducing drug rapamycin or physiological autophagy induced by nitrogen starvation to provide evidence that mitochondria are early targets of autophagic degradation in yeast, and we identified for the first time that a mitochondrial protein, Uth1p, is involved in this process.
Fig. 1. Deltauth1 strain is resistant to rapamycin. A and B, drop test. Cells were dropped in batches of 1000, 500, 100, and 50 cells on YPD (A) or YPL (B) medium with or without rapamycin (10 ng ml$^{-1}$). C and D, survival curves. Cells were grown aerobically in a YNB medium supplemented with 2% glucose (C) or 2% lactate (D). Rapamycin (0.2 µg ml$^{-1}$) was added and, at indicated times, aliquots of 500 cells were spread on YPD plates. The number of colonies was counted after a 3-day incubation at 28 °C. Each curve represents the average of 10 independent experiments; S.D. < 1%. ■, wild-type; □, Deltauth1; ◻, Deltaatg5.

Materials and Methods

Yeast Strains, Plasmids, and Growth Conditions—W303-1B (MATa, ade2, his3, leu2, trp1, ura3, can1) was used as the wild-type strain. The Deltauth1 strain was constructed from W303-1B as described previously (23). The Deltaatg5 strain was constructed by disruption of the ATG5 gene with the KanMX4 cassette in the W303-1B strain. Deltaep4, derived from the wild-type strain BY4742 (MATa, his3, leu2, ura3, met15), was obtained from Euroscarf (Frankfurt, Germany). For the measurement of ALP$^+$ activity, the PHO8 locus was replaced with PHO8Δ60 in each strain by transformation with an HindIII fragment of the plasmid pTN9 (a gift from Y. Ohsumi, National Institute for Basic Biology, Okazaki, Japan) bearing PHO8Δ60 as described previously (24). For fluorescent microscopy experiments the cells were transformed with the plasmid pGAL-CLbGFP containing the presequence of mitochondrial citrate peptidase 1; CCCP, carbonyl cyanide m-chlorophenylhydrazone; FM4-64-chlorophenylhydrazone; FM4-64 (final concentration of 40 nM) according to a modified method as described previously (29). mtGFP-expressing yeast cells stained with FM4-64 were visualized on a Leica microscope. The images were acquired with an SIS camera and processed with Corel Draw 9.0 suite software.

RESULTS

The Product of the UTH1 Gene Is Involved in the Response to Rapamycin—It has been shown previously that inactivation of the UTH1 gene induces resistance to rapamycin as well as to the heterologous expression of the human pro-apoptotic protein Bax, suggesting that Uth1p might be at the crossroads of different signals converging on mitochondria and leading to death (26).

Physiological autophagy induced by nitrogen starvation does not lead to cell death. On the contrary, strains impaired for autophagy, such as the Deltaatg5 mutant, do not survive nitrogen starvation for 15 h according to the method described (27). Fluorescence intensity was measured at 472 nm (excitation at 345 nm) in a Safas spectrophotometer. Protein concentration was measured with the Lowry method (28). ALP activities were expressed as arbitrary fluorescence units/min/mg protein.

Fluorescence Microscopy Measurements—Vacuoles were stained with N-(3-triethylammoniumpropyl)-4-(p-diethylaminophenyl-hexatrienyl) pyridinium dibromide (FM4-64; final concentration of 40 µM) according to a modified method as described previously (29). mtGFP-expressing cells stained with FM4-64 were visualized on a Leica microscope. The images were acquired with an SIS camera and processed with Corel Draw 9.0 suite software.

Western Blot Analyses—Protein samples preparation, SDS-PAGE, and Western blots were done as described previously (26). The primary antibodies used were mouse monoclonal anti-yeast Cox2p (1/2000; Molecular Probes), mouse monoclonal anti-yeast porin (1/2000; Molecular Probes), mouse monoclonal anti-yeast phosphoglycerate kinase (1/2000; Molecular Probes), goat polyclonal anti-aminopeptidase I (1/100; Santa Cruz Biotechnology), goat polyclonal anti-yeast Atg8p (1/250; Santa Cruz Biotechnology), and rabbit polyclonal anti-yeast actin (1/1000; Santa Cruz Biotechnology). Secondary anti-mouse, anti-rabbit, and anti-goat IgG antibodies coupled to horsedradish peroxidase (Jackson Laboratories) were used at 1/100000. An ECL+ kit (Amer sham Biosciences) was used for protein detection. Quantification of protein amounts was done using the ImageJ program (NCBI).

The abbreviations used are: ALP, alkaline phosphatase; API, aminopeptidase I; CCCP, carbonyl cyanide m-chlorophenylhydrazone; FM4-64, N-(3-triethylammoniumpropyl)-4-(p-diethylaminophenyl-hexatrienyl) pyridinium dibromide; mtGFP, mitochondria-targeted green fluorescent protein.
This resistance is more marked than that of the autophagy-deficient \( \Delta \text{atg5} \) mutant.

The effect of rapamycin was further assayed on the viability of cells grown on glucose (fermentation-dependent growth; Fig. 1C) or lactate-supplemented medium (respiration-dependent growth; Fig. 1D). Rapamycin induces a loss of viability of wild-type and \( \Delta \text{atg5} \) strains, but the \( \Delta \text{uth1} \) strain exhibited a strong resistance. It is noteworthy that this resistance was more marked on lactate-supplemented medium (Fig. 1D) where yeast cells develop large and fully active mitochondria, because this carbon source is exclusively oxidized by mitochondrial metabolic pathways (31). Whatever the carbon source, under nitrogen starvation conditions, a better survival rate was observed for the \( \Delta \text{uth1} \) strain in comparison with the wild-type, the autophagy-deficient \( \Delta \text{atg5} \) mutant, and the \( \Delta \text{pep4} \) mutant, which is deficient in the major vacuolar hydrolase, proteinase A (Fig. 2).

**Autophagic Machinery Is Not Affected in \( \Delta \text{uth1} \) Cells**—We were interested in examining the cellular autophagic activity in the \( \Delta \text{uth1} \) mutant to know if the observed resistance to rapamycin was due to a general blockage of the autophagic process. Several biochemical methods for assaying autophagy have been established. One improved method (24) is to follow the vacuolar delivery of the Pho8p, a cytosolic variant of the Pho8p alkaline phosphatase in which the membrane-spanning region and the vacuolar targeting sequence have been deleted. Such an N-terminal truncated Pho8p variant cannot be delivered to the vacuolar compartment via the normal secretory pathway and is only imported to the vacuole upon the induction of autophagy, when cells are shifted to nitrogen starvation conditions or treated with rapamycin. The vacuolar delivery of randomly sequestrated Pho8p in autophagic vesicles results in cleavage of the C-terminal propeptide in a proteinase B-dependent manner and activation of its enzyme activity. In our study, ALP activity was assayed in wild-type cells and \( \Delta \text{uth1} \) and \( \Delta \text{atg5} \) mutant strains grown on glucose (Fig. 3A) or lactate-supplemented (Fig. 3B) minimal medium after a 1-h rapamycin (0.2 \( \mu \)g/ml) treatment or 15 h of nitrogen starvation as described under “Materials and Methods.” ALP activities were expressed as arbitrary units-min\(^{-1}\)-mg\(^{-1}\) protein. Data are average \( \pm \) S.D. from 3–5 independent experiments.
cells were grown in a YNB medium containing 2% glucose to an A
duced processing of precursor API (prAPI). Wild-type and Δuth1
non-starved control culture (SD-N) was compared with that observed in the
these cultures after 15 h of starvation, and API processing was assessed
by immunoblot using a polyclonal antiserum specific for API. Process-
treatment (Fig. 1 D), exhibited intensely punctuated FM4-64
with some of them colocalizing with mtGFP as shown
served. Under the same conditions, ALP activity was signifi-
cessarily increased both in the wild-type and the Δuth1 strains
whatever the condition of induction. The highest autophagic
activity was found in starved Δuth1 mutant cells, when ALP
activity was increased five times.

Another method for measuring autophagic activity is to fol-
low the processing of the vacuolar aminopeptidase I (API) in
starved cells (33). API is synthesized on soluble ribosomes as a
61-kDa inactive precursor that is transported to the vacuole in
utrient-rich conditions by a constitutive non-classical vesicu-
lar transport mechanism, the cytoplasm-to-vacuole targeting
pathway, and is submitted to proteolytic maturation leading to
a 50-kDa form. Under starvation conditions or in presence of
rapamycin, API is transported to the vacuole by macroautoph-
agogy. Total protein extracts were prepared from cultures of
wild-type and Δuth1 strains grown on glucose-containing
medium and after 15 h of nitrogen starvation. An immu
blot with an antibody specific for API was done to monitor
precursor API processing (Fig. 4). Under starvation conditions,
only the mature form was visualized in wild-type and Δuth1
strains showing the activation of autophagy. Taken together,
these two sets of experiments (ALP activity and API matura-
ion) showed that the autophagy process was unaffected in the
Δuth1 mutant.

The Product of UTH1 Is Required for Vacuolar Degradation
of Mitochondria-Targeted GFP—According to the localization
of Uth1p in the external mitochondrial membrane (34), the
degradation of mitochondria was investigated further.

A construction expressing GFP fused downstream of the
targeting sequence of mitochondrial citrate synthase (mtGFP)
(25) was introduced in wild-type, Δuth1, and Δatg5 strains in
order to follow the behavior of mitochondria in situ. The
autofluorescent probe FM4-64, which specifically labels the
vacuolar membrane in yeast cells (29), was used simulta-
aneously. Under control conditions, wild-type cells grown on a
lactate and galactose-supplemented medium exhibit a well differen-
tiated mitochondrial network, and FM4-64 labeling shows the
presence of one or two large vacuoles (Fig. 5). Rapamycin
treatment of wild-type cells induced the disappearance of the
mitochondrial network and the appearance of patches predo-
nantly at the periphery of the cells. Most cells lost the classical
vacuolar membrane FM4-64 staining, and only few cells
showed faintly stained vacuoles. The proportion of cells in
which FM4-64 fluorescence was lost from vacuolar membranes
to give rise to diffused cytoplasmic staining corresponded with
the proportion of dead cells (85%; see Fig. 1 D). The remaining
15% of the cells, which were still viable after a 2-h rapamycin
treatment (Fig. 1 D), exhibited intensely punctuated FM4-64
staining, with some of them colocalizing with mtGFP as shown
in Fig. 5. The same perturbation of vacuolar membrane stain-
ing after rapamycin treatment was observed for glucose-grown
cells treated with rapamycin (data not shown).

The expression of mtGFP in Δuth1 and Δatg5 mutants also
revealed a normal mitochondrial network (Fig. 5). Opposite to
the case with wild-type, the addition of rapamycin to both
mutants did not induce any rapid disorganization of the mito-
chondrial network that remained intact after a 2-h treatment
(Fig. 5), and the network was marginally affected after a 6-h
treatment (not shown). No colocalization of mtGFP and
FM4-64 was ever observed in these strains. Interestingly,
FM4-64 staining of vacuolar membranes showed the presence
of a large number of small fragmented vacuoles in Δuth1 as
described in some mutants defective in vacuolar biogenesis and
autophagy, such as in the Δatg5 strain (Fig. 5) (35).

To verify that rapamycin treatment did not induce any side
effects by affecting mtGFP synthesis or import, cells were in-
cubated in the presence of cycloheximide (an inhibitor of pro-
tein synthesis) or carbonyl cyanide m-chlorophenylhydrazone
(CCCP; an uncoupler dissipating transmembrane electrical po-
tential). For the time of the experiment, the mitochondrial
network remained unaffected by these treatments in both the
wild-type (Fig. 6) and the Δuth1 strains (not shown).

Under conditions of physiologically induced autophagy by
nitrogen starvation, the appearance of patches of mtGFP at the periphery of the cells and the concomitant disappearance of the mitochondrial network were also observed in wild-type cells (Fig. 7). Moreover, co-staining with FM4-64 revealed the presence of some portion of mtGFP in the vacuoles (Fig. 7). Both phenomena were completely absent in control cells growing in rich medium (Fig. 5). In accordance with the deficiency of autophagy, no signs of mitochondria degradation were ever observed in ∆atg5 mutant cells under the same conditions (Fig. 7). In the culture of a ∆ath1 strain starved for 15 h, the following two distinct behaviors were observed: (i) About half of the cells exhibited normal FM4-64 staining and an intact mitochondrial network like that of the ∆atg5 mutant. (ii) The other half exhibited some hallmarks of a weak autophagy process, with patches of mtGFP at the periphery of the cells and vacuolar delivery of mtGFP but also the visible presence of a residual mitochondrial network (Fig. 7).

**Uth1p Is Required for the Early Vacuolar Degradation of Mitochondrial Proteins**—The time course of autophagic induction by rapamycin was also followed as the increase in the content of Atg8p, which is essential for the formation of autophagosomes (36, 37). In accordance with this observation, we observed an increase of the intracellular content of Atg8p after the addition of rapamycin in all tested strains growing under strict respiratory conditions (Fig. 8).

The amounts of several mitochondrial proteins localized in the outer (the mitochondrial porin Por1p) and inner (the cytochrome c oxidase subunit 2, Cox2p) mitochondrial membranes were followed by Western blot analyses in comparison with proteins localized in cytosol phosphoglycerate kinase (Pgk1p) and actin (Act1p) (Fig. 8). In the wild-type strain, the content of both mitochondrial proteins was strongly depressed 2 h after the beginning of rapamycin treatment and further decreased over a 6-h treatment. Under the same conditions, the amounts of cytosolic proteins were only marginally affected. When the wild-type cells were grown on glucose, this more rapid decrease of mitochondrial proteins was actually caused by vacuolar proteolysis and not by a blockade of their synthesis, the experiment was reproduced in a ∆pep4 strain (Fig. 8). The amounts of Por1p and Cox2p did not decrease after a 6-h rapamycin treatment, whereas in fact a slight increase was actually observed.

This lack of degradation in ∆pep4 cells confirms that the protein degradation observed in wild-type cells is executed in the vacuoles.

Rapamycin treatment of the autophagy-deficient ∆atg5 strain grown on lactate induced a higher increase of Atg8p in wild-type (Fig. 8); this is in accordance with the fact that the process of autophagosome formation and the subsequent vacuolar degradation of Atg8p is blocked in this mutant. Concerning mitochondrial proteins, no decrease in the amounts of Por1p and Cox2p was observed, but, as in the ∆pep4 mutant, a slight increase was recorded instead.

From this set of experiments it was seen that rapamycin treatment of cells grown under strict respiratory conditions induces the early degradation of mitochondrial proteins by a process that requires the following: (i) the formation of autophagosomes; and (ii) vacuolar proteolysis. During the short course of the experiment cytosolic proteins remain poorly affected, suggesting that fully differentiated organelles like mitochondria are early targets of the rapamycin-induced process. Also, Por1p and Cox2p, which are localized on different membranes, are degraded together, suggesting that whole mitochondria are targeted by the process.

In accordance with the resistance of the ∆ath1 strain to rapamycin (Fig. 1), degradation of the two mitochondrial proteins was largely impaired in this strain (Fig. 8). On the other hand, the product of ATG8 increased up to a level similar to that of the wild-type strain (Fig. 8), confirming the conclusion drawn from the measurement of ALP activity (Fig. 3) and API processing (Fig. 4) that the autophagic process is still active. This supports the view that the resistance of the ∆ath1 strain is not caused by a general defect in the autophagic machinery but that the mitochondrial degradation targeted by this machinery is delayed.

**DISCUSSION**

Data reported in this paper allowed us to identify conditions where a rapid degradation of mitochondria by rapamycin treatment or nitrogen starvation growth could be visualized. Within 2 h of rapamycin treatment, mitochondrial proteins are de-
graded in a way that depends on the following: (i) autophagosome formation, because it is prevented by atg5-inactivation; and (ii) vacuolar degradation, because it is prevented by pep4 inactivation. This degradation of mitochondrial proteins correlates with the disappearance of the mitochondrial network and the appearance of a mitochondrial/vacuole co-staining. This mitochondrial degradation does not occur in strains impaired for autophagy such as the Δatg5 mutant. Opposite to the case with the Δatg5 mutant, the autophagic machinery remains fully active in Δuth1 mutant, but mitochondria degradation by this process is delayed. These results showed that the mitochondrial protein Uth1p is involved in autophagic mitochondrial degradation.

This protein, Uth1p, has been initially found in a genetic screen aiming to identify proteins involved in the regulation of the yeast life span (38). Furthermore, it was found to be a member of the so-called “SUN” family, which includes four proteins having a very high degree of identity (23, 39). The product of UTH1 exhibits some remarkable properties. It is mainly localized in the mitochondrial outer membrane (34) but was also found in the cell wall (34, 40). This alternative cell wall localization is likely to have a physiological meaning, because it can be selectively suppressed by point mutations in the protein.2 The absence of Uth1p does not have dramatic consequences under normal growth conditions; it induced a 15–25% decrease of mitochondrial cytochromes as well as other mitochondrial enzymes and an increase of growth yield (23).

More recently, Uth1p was found to be involved in yeast cell death induced by the heterologous expression of the human proapoptotic protein Bax (26). In mammalian cells, Bax targets the mitochondrial outer membrane, where it induces the formation of a large channel likely involved in the mitochondria-to-cytosol relocalization of cytochrome c (42–44). Bax-induced characteristics in yeast resemble apoptotic like hallmarks induced by H2O2 treatment (45) in which a caspase-like activity might be involved (46). However, cytochrome c release is not mandatory to Bax-induced cell death in yeast (47). In addition, because Uth1p is not involved in the mitochondrial targeting of Bax or in cytochrome c release activity (26), we proposed that Bax was able to activate an alternative death-inducing pathway involving Uth1p. As a matter of fact, Uth1p overexpression was found to induce cell death, and uth1 inactivation induced a resistance of growth to rapamycin (26). These observations suggested that Uth1p might be involved in a death pathway related to autophagy.

The observation reported in the present paper that Uth1p is involved in the autophagic degradation of mitochondria induced by rapamycin or nitrogen starvation supports this hypothesis. Clearly, Uth1p does not participate in the autophagic machinery, because the biochemical hallmarks related to this process (ALP activation and API processing) are as active as those in wild-type, in contrast to the behavior of the autophagy-deficient strain Δatg5. More likely, Uth1p might be involved in the recognition of mitochondria by the autophagic machinery. However, it should be noted that, both from viability and fluorescence microscopy experiments, about half of Δuth1 cells are still able to undergo normal mitochondria autophagy, suggesting that Uth1p may not be the only protein involved in the process.

The degradation process termed autophagy covers distinct, although related, phenomena. The best characterized, and also the less specific, is the macroautophagy of large parts of the cytoplasm including the organelles (reviewed in Ref. 2). However, more selective phenomena were also evidenced. As an example, microautophagy of the nucleus via the physical contact between nuclei and vacuoles was shown to involve selective protein-protein interactions such as Nvj1p on the nuclear envelope and Vac8p on the vacuolar membrane (5). This process does not involve the well established components of macroautophagy signaling but is still under the control of the TOR (target of rapamycin) kinase pathway. Another example of selective autophagy was observed in the methylotrophic yeast Pichia pastoris, where peroxisomes can be selectively degraded

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by vacuoles in a way independent from macroautophagy (3). The degradation of other organelles has not been investigated to date, but tools such as selectively targeted GFP and specific antibodies are now available for such studies.

Concerning yeast mitochondria, since the first report that they could be engulfed by the macroautophagy machinery (15), one study has suggested that a selective mechanism of mitochondrial autophagy also occurred in yeast, i.e., inactivation of the mitochondrial AAA-type protease Yme1p leads to a vacuole-dependent mitochondria-to-nucleus transfer of genetic material (21, 22). However, the molecular basis of this transfer has not been identified to date.

The finding that Uth1p is a component involved in the early selective degradation of mitochondria is now a basis for the identification of the other components involved in the autophagic degradation of mitochondria. This might be of general interest, not only in yeast but also, given the recent evidence of connections between apoptosis and autophagy, in mammalian cells (48).

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