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Transcriptional and post-transcriptional regulation of autophagy in the yeast *Saccharomyces cerevisiae*

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Autophagy is a highly conserved catabolic pathway that is vital for development, cell survival, and the degradation of dysfunctional organelles and potentially toxic aggregates. Dysregulation of autophagy is associated with cancer, neurodegeneration, and lysosomal storage diseases. Accordingly, autophagy is precisely regulated at multiple levels (transcriptional, post-transcriptional, translational, and post-translational) to prevent aberrant activity. Various model organisms are used to study autophagy, but the baker's yeast *Saccharomyces cerevisiae* continues to be advantageous for genetic and biochemical analysis of non-selective and selective autophagy. In this Minireview, we focus on the cellular mechanisms that regulate autophagy transcriptionally and post-transcriptionally in *S. cerevisiae*.

Overview

In response to external environmental and internal homeostatic cues, cells must efficiently and successfully adapt to ensure survival during stress conditions. Macroautophagy/autophagy is a highly conserved (from yeast to human) catabolic mechanism of "self-eating" that is vital for homeostasis, development, and the clearance of damaged or superfluous organelles and protein aggregates, substrates that cannot be degraded by the proteasome, the other major degradative pathway in eukaryotic cells. Autophagy occurs in all eukaryotic cells (1), underlying its importance. The classical morphological feature of autophagy is the formation of the double-membrane structure termed the autophagosome. In most cells, basal autophagy generally occurs at a low level but is markedly induced in response to nutrient deprivation, pathogen infection, and other forms of stress. Autophagic flux results in the fusion of the autophagosome with the vacuole (in yeast or plants) or a lysosome (in mammalian cells). In yeast, vacuolar hydrolases degrade the autophagic cargo. This degradation is followed by efflux of the breakdown products for reuse, helping to safeguard cell survival particularly during starvation or low-energy conditions.

When induced by nutrient deprivation or pharmacological means, non-selective autophagy targets bulk cytoplasm for uptake into the phagophore, the autophagosome precursor. During selective types of autophagy, the phagophore sequesters specific cargo (such as organelles or invasive pathogens) through receptor-mediated interactions between selective autophagy receptors and Atg8 (which is located on both sides of the phagophore), and unique cargo-localized ligands, thereby generally excluding bulk cytoplasm. In addition to receptor targeting, specific cargos are further selected by proximity to the expanding phagophore membrane (2). In yeast, under nutrient-rich conditions, a biosynthetic form of selective autophagy, the cytoplasm-to-vacuole targeting (Cvt)[2] pathway, delivers resident hydrolases to the vacuole (3–6). Multiple forms of selective autophagy in yeast have been characterized, including mitophagy (7, 8), pexophagy (9), reticulophagy (10, 11), ribophagy (12), granulophagy (13), aggrephagy (14), nucleophagy (11, 15), lipophagy (16, 17), and piecemeal microautophagy of the nucleus/micronucleophagy (18, 19). Although not considered to be a selective type of autophagy, the degradation of bulk RNA has also been described (20). At least in yeast, the receptors utilized to target cargos are unique to the form of selective autophagy that the cell is undergoing (5, 7, 8, 21). For further discussion on the topic of selective autophagy, see Refs. 22, 23.

Autophagy is a highly complex and rigorously coordinated process; at present, 41 unique autophagy-related (*ATG*) genes have been identified in fungi, and many have homologs in higher eukaryotes. Autophagy dysregulation is associated with multiple human pathologies such as cancer, neurodegeneration, microbial infection and lysosomal storage diseases. Thus, autophagy must be strictly modulated to maintain an appropriate level, as too much or too little can be deleterious to the cell. Accordingly, eukaryotic cells have evolved mechanisms to tightly control and coordinate autophagy at multiple levels (transcriptional, post-transcriptional, translational, and post-translational; see Fig. 1). In this Minireview, we focus on autophagy regulation, particularly at the transcriptional and post-transcriptional levels, in the yeast *Saccharomyces cerevisiae.* In addition to its high degree of conservation with other systems, *S. cerevisiae* continues to be particularly advantageous for genetic and biochemical analysis of non-selective and selective forms of autophagy.

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[2] The abbreviations used are: Cvt, cytoplasm-to-vacuole targeting; TOR, target of rapamycin; miRNA, microRNA; PAS, phagophore assembly site; Ubl, ubiquitin-like; bZIP, basic leucine zipper.

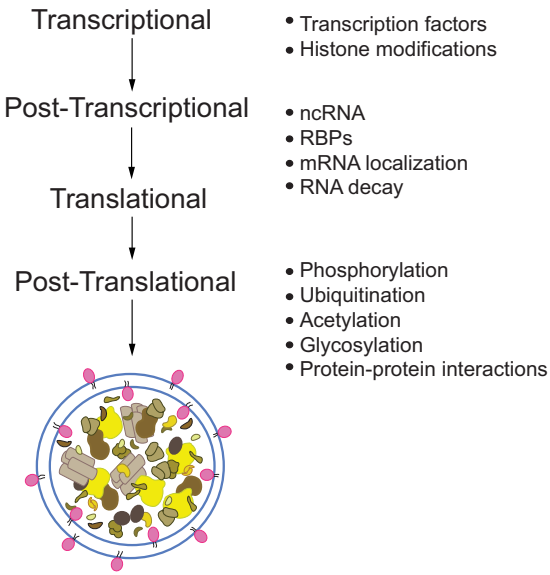

Figure 1. Autophagy regulation occurs at multiple levels. Because of the essential role that autophagy plays in maintaining homeostasis and the myriad of diseases that can result from perturbations to the pathway, cells must strictly modulate the entire process, beginning at transcription through post-translational modification. At the level of transcription, *ATG* gene expression can be regulated both positively and negatively through the action of specific transcription factors and epigenetic changes at histones. These transcripts can then be controlled further at the post-transcriptional and translational levels through the mechanisms of non-coding (*nc*) RNA, RNA-binding proteins (*RBPs*), mRNA localization, and RNA decay. At the protein level, post-translational modification such as phosphorylation, ubiquitination, acetylation, glycosylation, and protein–protein interactions can further regulate autophagy activity.

Autophagy is a dynamic process that requires constant fine-tuning at multiple levels to maintain the appropriate timing of induction and magnitude within the cell. Cells control the level of the autophagic response largely by regulating the size and frequency (*i.e.* number) of autophagosomes (24, 25). Here, we will briefly describe the main phases of the autophagic process and the machinery involved before further reviewing recently published work on its transcriptional and post-transcriptional regulation.

Autophagy in *S. cerevisiae*

There are five main stages of autophagy, including: 1) induction and nucleation of the phagophore membrane; 2) expansion of the phagophore; 3) closure and maturation to form the autophagosome; 4) autophagosome–vacuole fusion; and 5) degradation/efflux of the breakdown products (see Fig. 2). Briefly, in yeast, autophagy is typically stimulated through nutrient deprivation (most commonly with nitrogen starvation) or with the use of a pharmacological agent such as rapamycin. Rapamycin treatment inhibits target of rapamycin (TOR), a serine/threonine kinase and major negative regulator of autophagy induction in yeast (26). In addition to TOR, upstream nutrient sensors such as protein kinase A and Snf1 (the homolog of mammalian AMP kinase) integrate signals for autophagy regulation (27). In yeast, the phagophore assembly site (PAS) is the intracellular location of autophagosome formation. At the PAS, Atg proteins assemble in a hierarchical order. The first complex recruited to the PAS includes Atg1, Atg13, and the Atg17–Atg31–Atg29 ternary subcomplex (28, 29). Next, Atg9 (along with Atg2 and Atg18) localizes to the PAS (30). The phagophore, a dynamic cup-shaped membrane structure, transiently envelops bulk cytoplasm or specific cargo. This sequestration event is followed by expansion and closure of the phagophore to form the mature autophagosome and requires two conserved ubiquitin-like (Ubl) conjugation systems, which involve Atg12 and Atg8.

The Atg12 Ubl system includes Atg5, Atg7, Atg10, Atg12, and Atg16 and leads to the formation of the heterotrimeric complex Atg12—Atg5–Atg16, which may function as an E3-like enzyme for the Atg8 conjugation system, although this complex is not absolutely required for conjugation to occur (31–34). The conjugation of Atg12 to Atg5 at the phagophore occurs sequentially, requiring Atg7, an E1-like enzyme that activates Atg12, and Atg10, an E2-like enzyme (35, 36). The Atg8 Ubl system is necessary for membrane expansion and closure of the phagophore, and this second system includes Atg3, Atg4, Atg7, and Atg8 (30). Non-lipidated Atg8 is converted to its lipidated phosphatidylethanolamine-conjugated species following Atg4-mediated proteolytic processing of its C terminus, Atg7-dependent activation, and Atg3-facilitated conjugation at a conserved C-terminal glycine (37, 38).

The next major step in autophagy involves fusion between the outer membrane of the autophagosome and the vacuole. The resulting vesicle formed by this event is termed the autophagic body and consists of the remaining inner autophagosome membrane found within the vacuole lumen. The final events in autophagic flux include degradation of the cargo, followed by efflux of the resulting macromolecules. In yeast, the vacuole has enzymes for degrading the major macromolecules; however, an efflux mechanism has only been identified for amino acids (39), and catabolized RNA products appear to be secreted from the cell (20). For a more comprehensive review on the main stages of autophagy and the role of ubiquitin, please see Refs. 28, 40, 41.

Transcriptional regulation of autophagy

Background

As mentioned above, cells must successfully fine-tune and integrate signals at multiple regulatory levels to maintain appropriate control over autophagy. Here, we focus on transcriptional and post-transcriptional regulation of autophagy in *S. cerevisiae*. For further discussion on autophagy regulation, particularly at the epigenetic and post-translational levels, please see these recent reviews in Refs. 40, 42–45.

Major transcriptional regulators in yeast

Ume6—Ume6 is a DNA-binding protein that has dual functions both as a transcriptional activator and as a repressor depending on the growth conditions (46, 47). Ume6 is dependent on the corepressor Sin3 and histone deacetylase Rpd3, and all are components of the multisubunit Rpd3 large (Rpd3L) complex in yeast (48–50). Rpd3L is one of the 2 Rpd3 histone deacetylase complexes that regulate gene expression (50–52). A Ume6 consensus-binding site (URS1 region) is found within the *ATG8* promoter (53); Ume6 directly binds (and thereby represses) the *ATG8* promoter under nutrient-rich conditions (53). Ume6 undergoes phosphorylation by the kinase Rim15

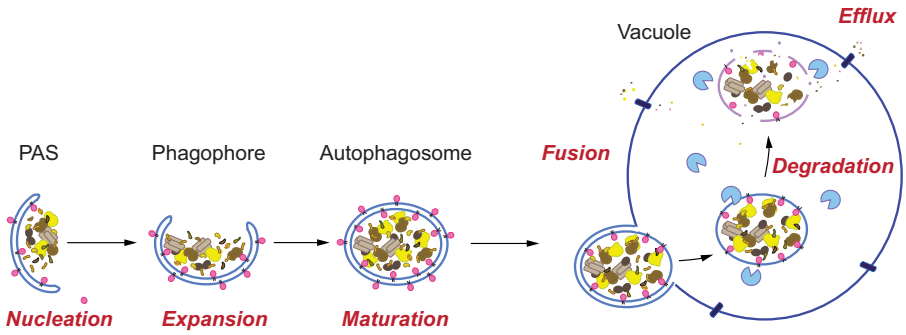

Figure 2. Non-selective autophagy in *S. cerevisiae*. Autophagy occurs through a sequential series of events in the yeast *S. cerevisiae,* including induction and nucleation of the phagophore at the PAS, expansion of the phagophore, closure and maturation to form the autophagosome, autophagosome–vacuole fusion, and cargo degradation followed by efflux of the breakdown products.

(further detailed below) during nitrogen starvation, which leads to the derepression of *ATG8*, thus promoting *ATG8* transcription (53). Deletion of *UME6*, *SIN3*, and/or *RPD3* significantly up-regulates *ATG8* mRNA (and consequently protein) under nutrient-rich conditions, and autophagy is more rapidly induced in *ume6*Δ cells during nitrogen starvation (53). Importantly, the amount of Atg8 directly correlates with the size of autophagosomes during starvation conditions (24). These findings support a mechanism whereby the cell is primed for a rapid autophagic response once it encounters starvation conditions. Although Ume6 is not conserved in more complex eukaryotes, the mammalian SIN3 proteins appear to play a similar role in regulating the expression of the Atg8 homolog MAP1LC3B (53).

Pho23—Pho23 is another member of the Rpd3L complex (50, 54) and a negative regulator of autophagy activity in yeast (25). Deletion of *PHO23* results in the up-regulation of multiple *ATG* transcripts, including *ATG1*, *-7–9*, *-12*, *-14,* and *-29* and an increased frequency of autophagosome formation (*i.e.* number) (25). Pho23 represses *ATG9* under nutrient-replete conditions, and levels of Atg9 directly affect the frequency of autophagosome formation (25). Atg9 is the only integral membrane protein component of the core autophagy machinery—those proteins that are essential for autophagosome formation (55). Atg9 cycles between the PAS and peripheral sites close to the mitochondria during autophagy; these sites are also known as tubulovesicular clusters and are thought to correspond to donor membranes (56–58). Phosphorylation of Atg9 at serine 122 (Ser-122) regulates anterograde movement between the peripheral sites and the PAS, thereby controlling the rate of autophagosome formation (59). These data support a model in which Atg9 functions to provide membrane or to direct membrane delivery for phagophore expansion; thus, increased levels of Atg9 (through Pho23 derepression) allow for a greater number of autophagosomes to form, which would have a direct effect on the magnitude of autophagy activity.

Rph1—Rph1 is a Jumonji C catalytic domain-containing histone demethylase (60). However, the role of Rph1 in autophagy is independent of its demethylase activity (61). Deletion of *RPH1* enhances autophagy, and overexpression of Rph1 strongly inhibits autophagy and autophagosome formation (61). Rph1 functions as a negative transcriptional regulator of autophagy by repressing the expression of a subset of *ATG* genes under nutrient-replete conditions, particularly *ATG7,* but also including *ATG1, -8, -9, -14, -29,* and *-32* (61). Furthermore, Rph1 directly regulates *ATG7* by binding to its promoter; this binding does not occur when the DNA-binding domains of Rph1 are eliminated (61). As described above, Atg7 plays an essential role in the conjugation of phosphatidylethanolamine to Atg8, which is critical for autophagosome formation. Levels of Atg7 have an impact on the magnitude of the autophagic response (61, 62). When cells are starved for nitrogen, Rim15 phosphorylates Rph1, inhibiting its repression of *ATG* transcripts (61). KDM4A, a mammalian homolog of Rph1, has a conserved role in autophagy induction (61). Additionally, Rph1 may mediate transcriptional control over other as yet unidentified *ATG* genes (63).

Rim15—The Rim15 protein kinase integrates signals from the two major nutrient sensing pathways in yeast, TOR and protein kinase A, to positively regulate autophagy (64–65). Although not a direct transcriptional regulator, Rim15 phosphorylates the DNA-binding proteins Ume6 (53) and Rph1 (61) to influence *ATG* gene transcription (66); Rim15-dependent phosphorylation inhibits these transcription factors, leading to the derepression of *ATG* genes (61). Future studies will determine whether Rim15 mediates the phosphorylation of additional autophagy regulatory factors, particularly those involved in other aspects of transcriptional or post-transcriptional autophagy modulation.

Gcn4—Gcn4 is a basic leucine zipper (bZIP) transcriptional activator that primarily binds to the 5′-TGACTC-3′ consensus site in the promoter regions of target genes (67). Gcn4 was initially identified to function in the amino acid starvation response and has been described as a principal regulator of autophagy gene expression (68). During growing conditions, Gcn4 positively mediates delivery of precursor aminopeptidase I in the Cvt pathway (69). When cells undergo starvation, Gcn4 regulates non-selective autophagy activity through *ATG* gene transcription (69). Gcn4 activates *ATG1*, *ATG13,* and *ATG14* gene expression during amino acid deprivation (68) and *ATG1* during nitrogen starvation (69). Gcn4 controls *ATG41* mRNA expression during nitrogen starvation-induced autophagy through transcriptional activation (70). Recently, Atg41 was identified to function in Atg9 cycling and the delivery of donor membrane to expand the phagophore at the PAS (70). The translation of *GCN4* is stimulated by the phosphorylation of Sui2/eIF2α by the protein kinase Gcn2 (71). Gcn2 itself also positively regulates autophagy, presumably by its downstream

effects on Gcn4-mediated *ATG* transcription (72, 73) and possibly through the inhibition of TOR (74).

Gln3—Gln3 is a GATA-like transcription factor that shares only 65% homology with other known GATA factors in yeast (75, 76). Gln3 binds to the consensus sequences 5′-GATAAG-3′ and 5′-GATTAG-3′, which have been previously identified as nitrogen-responsive upstream activation sequences within the promoter regions of target genes (77). During rich conditions, Gln3 mediates biosynthetic delivery of precursor aminopeptidase I to the vacuole (69). When cells are starved, Gln3 positively regulates non-selective autophagy by targeting *ATG14* (78), *-7–9*, *-29*, and *-32* (69). Unexpectedly, in nutrient-replete conditions, deletion of *GLN3* results in the accumulation of *ATG8* and *ATG29* transcripts, demonstrating either direct or indirect negative control over basal autophagy (69).

Gat1—Gat1 is another GATA-type transcription factor that has a GATA1-type zinc finger DNA-binding motif and binds to 5′-GATAAG-3′ upstream activation sequence regions in the promoters of nitrogen-sensitive genes, similar to Gln3 (79). Gat1 functions as a positive factor for autophagy induction; deletion of *GAT1* results in decreased autophagy activity (69). Also similar to Gln3, deletion of *GAT1* significantly down-regulates *ATG7–9*, *-29*, and *-32* mRNAs; however, no additive effect is observed on *ATG* transcript levels when both *GAT1* and *GLN3* are deleted in the same strain (69).

Other transcriptional regulators—Yap1 is a bZIP transcription factor with a preference for binding at promoter sites containing 5′-TTACTAA-3′ sequences (80). It has been recently reported that Yap1 positively regulates transcription of the lipase gene *ATG15* during starvation-induced autophagy (81). Atg15 preferentially hydrolyzes phosphatidylserine and facilitates autophagic body lysis within the vacuole (82, 83). Sfl1 functions as a transcriptional repressor and activator (84, 85) and has also been recently identified to function as a positive regulator of the Cvt pathway, autophagy, and *ATG8* expression (69). Fyv5 negatively regulates the expression of *ATG1*, *-8*, *-9*, and *-14*, but this effect may not be direct; in contrast, the Cvt pathway appears to be positively affected by this factor (69). Spt10, a histone H3 acetylase, represses *ATG8* and *ATG9* at both the RNA and protein levels (69). Although key transcriptional regulators have been identified to affect core *ATG* gene transcripts, the potential exists for novel factors to be discovered, particularly those that may target selective autophagy pathways.

Post-transcriptional regulation of autophagy

Background

Although novel transcriptional mediators of autophagy have recently been identified (25, 53, 61, 69), post-transcriptional regulation of autophagy in yeast is largely uncharacterized. In mammals, non-coding RNAs such as microRNAs (miRNAs) and RNA-binding proteins can modulate autophagy at the post-transcriptional level (42, 45, 86–89). However, the RNA interference system (which is required for miRNA processing (90, 91)) is not present in *S. cerevisiae* (92). Alternatively, another mechanism whereby cells exert post-transcriptional control over gene expression is through RNA decay pathways (which can degrade transcripts in either the 5′ to 3′ or the 3′ to 5′ direction). During canonical 5′ to 3′ degradation, transcripts undergo a reversible process known as deadenylation (which removes the 3′ poly(A) tail), followed by decapping. The decapping enzyme Dcp2 removes the 5′-methylguanosine cap of the mRNA, resulting in an exposed 5′-monophosphate. Finally, the decapped cytoplasmic mRNAs undergo 5′- to 3′-mediated degradation by the cytoplasmic exoribonuclease Xrn1.

Dcp2 and RCK family RNA helicases Dhh1/Vad1/DDX6

A role has recently been described for Dcp2 and RCK family RNA-binding proteins as post-transcriptional regulators of *ATG* mRNAs, autophagy, and autophagy-dependent innate immune responses in yeast and mammalian cells (93). RCK family members–Dhh1 in *S. cerevisiae*, Vad1 in *Cryptococcus neoformans,* and DDX6/p54 in mammals–are RNA helicases acting in part as decapping accessory factors that interact with target mRNAs through recruitment to the decapping complex by binding the 5′- and/or 3′-untranslated region of selected transcripts (40, 94). Dhh1 also physically interacts with the decapping enzyme Dcp2 (95).

In the report by Hu *et al.* (96), deletion of *DHH1* or a temperature-sensitive (*ts*) mutation of *DCP2* caused a significant up-regulation of *ATG* transcripts. In particular, of the *ATG* transcripts that were examined in this study, *dhh1*Δ cells demonstrated significantly increased levels of *ATG3, -7, -8, -19, -20, -22,* and *-24* mRNA under nutrient-replete conditions (96). In the *dcp2-7*Δ *ts* strain, transcript levels for *ATG1* through *ATG9, ATG11, ATG13* through *ATG24,* and *ATG29, -31, -32,* and *-34* were significantly up-regulated in rich conditions (96). Both the *dhh1*Δ and *dcp2-7*Δ *ts* strains demonstrated higher levels of autophagy activity through multiple assays when starved for nitrogen (96). This mechanism is highly conserved across the two fungal species examined (*S. cerevisiae* and the pathogen *C. neoformans*) and up through mammalian cells (96). In *C. neoformans*, the Dhh1 homolog Vad1 mediates decapping of *ATG* mRNAs, especially *ATG8* (96). Furthermore, Hu *et al.* (96) demonstrated that Dcp2 is phosphorylated by TOR under nutrient-rich conditions in *C. neoformans,* which drives its association with (at least) *ATG8* mRNA, stimulating recruitment of the transcript to the decapping machinery, followed by subsequent decapping. Thus, TOR acts as a negative regulator of the translation of *ATG* genes under conditions where it promotes the translation of the vast majority of cellular transcripts. In mammalian cells, mechanistic TOR phosphorylates DDX6, the homolog of Dhh1/Vad1, resulting in decapping of the *MAP1LC3B* transcript under nutrient-rich conditions to repress autophagy (96). Transcripts are then presumably degraded to maintain autophagy at a basal level. In contrast, starvation conditions inactivate TORC1, arresting degradation of the targeted transcripts and promoting sustained autophagy (96).

Xrn1

The data on Dhh1/Vad1 and Dcp2 imply a role for 5′ to 3′ mRNA degradation in autophagy regulation. Recent work shows that the RNase Xrn1/XRN1, which functions downstream of the decapping complex in the canonical 5′ to 3′ RNA

decay pathway, is also a negative post-transcriptional regulator of autophagy in both yeast and mammalian cells (97). Chromosomal deletion of *XRN1* induces a more rapid and robust autophagy response as determined through multiple assays in yeast (97). We also found that the frequency of autophagosome formation increases in starved *xrn1*Δ cells compared with wild-type cells based on transmission electron microscopy (97). Furthermore, when *xrn1*Δ cells are assessed by quantitative PCR under nutrient-rich conditions, select *ATG* transcripts are found to be up-regulated, including *ATG1*, *-4*, *-5*, *-7*, *-8*, *-12*, *-14*, *-16*, *-29*, and *-31*. Regulation of (at least) *ATG8*, *ATG12*, and *ATG29* is dependent upon the RNase activity of Xrn1 (97).

In mammalian cells, there is enhanced autophagy activity in a starvation-independent manner when XRN1 is depleted by small interfering RNA (97). The impact on autophagy is blocked in *BECN1* or *ATG5* CRISPR knockout cells, supporting the role of the canonical autophagy pathway (97); BECN1 is a component of the phosphatidylinositol 3-kinase complex required for autophagy induction (98). In addition, reduction of XRN1 levels is associated with an up-regulation of poliovirus infection in an autophagy-dependent manner (97), underlying the role of Xrn1/XRN1 as a conserved autophagy regulator. Poliovirus, similar to other picornaviruses, utilizes host membranes that are proposed to be derived from autophagosomes to support viral genome replication (97, 99, 100).

Summary

The studies by Hu *et al.* (96) and Delorme-Axford *et al.* (97) provide a paradigm for post-transcriptional autophagy regulation, but they also represent the limit of what is known about this type of regulation of autophagy in yeast. Although these findings are exciting and novel, it is still not clear why there appears to be differential targeting of transcripts in the strains examined (*dcp2–7*Δ *ts*, *dhh1*Δ, and *xrn1*Δ) even though they encode components of a related pathway of RNA degradation (96, 97). Thus, despite these insights, much work remains to further understand how autophagy is controlled post-transcriptionally. For example, how are transcripts selected for degradation under nutrient-replete conditions? Although Dhh1 and Xrn1 are likely to drive some degree of specificity, many more *ATG* transcripts are affected in the *dcp2-7*Δ *ts* cells compared with the *dhh1*Δ and *xrn1*Δ strains (96, 97). Based on these data, Dhh1 and Xrn1 are likely not the only factors mediating selective transcript targeting. Furthermore, although *S. cerevisiae* does not post-transcriptionally regulate gene expression through miRNA, additional non-coding RNA mechanisms such as long non-coding RNA could potentially play a role in autophagy regulation. Future studies should be aimed toward uncovering additional components moderating *ATG* gene expression through RNA decay.

Conclusions

Here, we present a concise review of what is currently known regarding the transcriptional and post-transcriptional regulation of autophagy in the yeast *S. cerevisiae* (see Fig. 3 for a summary). Recent advances in the field have provided additional clues as to the myriad of regulatory mechanisms that cells maintain to tightly control and coordinate autophagy. However, many questions remain, particularly concerning how autophagy is regulated post-transcriptionally, not only in yeast but in other eukaryotic systems as well. Additional novel post-transcriptional regulatory factors have yet to be identified and characterized. Further investigation into the mechanisms by which cells control the major stages of autophagy—especially induction and magnitude—at multiple regulatory levels is critical to enhance our understanding of how this essential process is maintained in the cell to promote normal physiological processes and how its dysregulation contributes to disease pathogenesis.

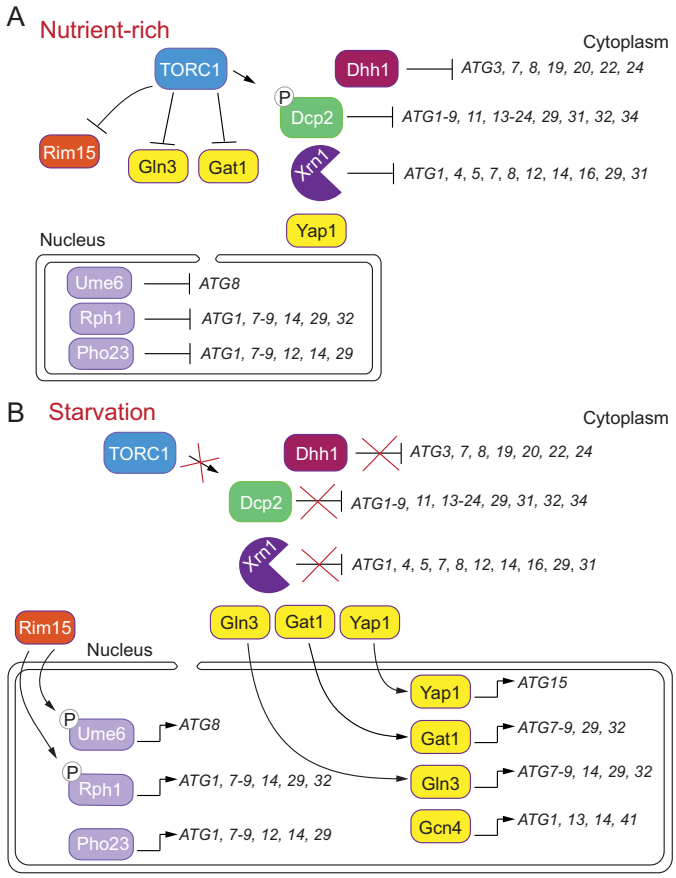

Figure 3. Summary of transcriptional and post-transcriptional regulatory factors in *S. cerevisiae*. *A*, during nutrient-replete conditions, TORC1 is active and negatively regulates key autophagy-promoting factors, such as Rim15, while activating negative regulatory elements, including the decapping enzyme Dcp2. Dcp2 mediates decapping of target transcripts for subsequent RNA degradation. Repressors such as Rph1, Ume6, and Pho23 bind the promoters of *ATG7*, *ATG8*, and *ATG9*, respectively, to maintain autophagy at a basal level. *B*, when autophagy is stimulated by an external stress, such as nitrogen or amino acid starvation, TORC1 becomes inactivated. This inhibition of TORC1 allows for the downstream activation of positive autophagy regulators. Activators such as Gcn4, Gln3, Gat1, and Yap1 bind to target genes for transcription as indicated. RNA decay mediators Dhh1, Dcp2, and Xrn1 no longer target *ATG* mRNAs for down-regulation; instead, these *ATG* transcripts are presumably translated to sustain autophagy.

Acknowledgment—We apologize to those whose work was not included here due to space limitations.

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