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COMMENTARY

Small GTPase proteins in macroautophagy

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ABSTRACT

Macroautophagy, a highly conserved process in eukaryotic cells, is initiated in response to stress, especially nutrient starvation. Macroautophagy helps cells survive by engulfing proteins and organelles into an unusual double-membraned structure called the autophagosome, which then fuses with the lysosome. Upon degradation of the engulfed contents, the building blocks are recycled for synthesis of new macromolecules. Recent work has demonstrated that construction of the autophagosome requires a variety of small GTPases in variations of their normal roles in membrane traffic. In this Commentary, we review our own recent findings with respect to 2 different GTPases, Arl1, a member of the Arf/Arl/Sar family, and Ypt6, a member of the Rab family, in the yeast *S. cerevisiae* in light of other information from the literature and discuss future directions for further discerning the roles of small GTPases in autophagy.

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Introduction

Macroautophagy is a process by which defective proteins or organelles are packaged and transported for breakdown in lysosomes (called vacuoles in the yeast *Saccharomyces cerevisiae*) so that building blocks (amino acids, lipids, etc.) can be recycled for reuse, especially under stress conditions such that induced by nitrogen starvation. Activation of this pathway, initiated by inhibition of the Tor complex results in the construction of an unusual double-membraned structure called the autophagosome, which grows from a structure called the phagophore at the phagophore assembly site (PAS). As macroautophagy proceeds, the autophagosomes fuse with the lysosome/vacuole then the inner membrane as well as the engulfed contents are broken down by degradative enzymes contained in the lysosome/vacuole.[1,2]

Packaging of material into autophagosomes is a complex process requiring membranes from a number of different organelles, including the ER, Golgi apparatus, plasma membrane and mitochondria.[3] Construction and then consumption of autophagosomes require a number of proteins specific to autophagy, the Atg proteins. Finally, small GTPases of the Arf/Arl/Sar and Rab families are required for both construction of the autophagosome and fusion of the autophagosome with the lysosome (or vacuole in yeast) in a variation of their roles as membrane traffic regulators for the secretory pathway and endocytosis.[4-7] In this Commentary, we will describe our recent work documenting roles for 2 GTPases in macroautophagy, Arl1, a member of the Arf/Arl/Sar family of small GTPases, and Ypt6, a member of the Rab family, in *S. cerevisiae*,[8] describe how these data fit into a larger understanding of the roles of membrane traffic in macroautophagy, then discuss future directions. We will focus primarily on what has been learned from studies in yeast, but note that this process is highly conserved across eukaryotes, including higher plants and animals.

The roles of yeast ARL1 *and* YPT6 *in macroautophagy*

Arl1, highly conserved in eukaryotes, is involved in membrane traffic in the secretory and endocytic pathways.[9,10] Arl1 is also a mediator of K^+ homeostasis in yeast,[11-13] although it is unknown whether Arl1 plays a similar role in other eukaryotes.

Our interest in exploring a potential role for Arl1 in macroautophagy was initially sparked by results describing a role for *ARL1* in autophagic cell death in *S. cerevisiae*,[14] specifically, that a mutant allele of *ARL1*, *ARL1[D151G]* extended the viability of a *cdc28* mutant. By using specific autophagy assays, the GFP-Atg8 assay,[15]

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which measures transfer of a key regulator of autophagy, Atg8 to the vacuole by examining whether free GFP is produced; and the Pho8Δ60 assay,[16] which measures arrival of phosphatase activity in the vacuole by autophagy, we found that an *arl1*Δ mutant was unable to perform autophagy under certain conditions. Specifically the defective autophagy phenotype was only observed at the restrictive temperature of 37°C; autophagy proceeded normally at the permissive temperature, 30°C. In addition, the phenotype was fully reversible upon reincubation of the cells at 30°C.[8]

Because *YPT6* exhibits synthetic lethality with *ARL1*,[17] we also explored the potential role of *YPT6* in macroautophagy, and found a similar phenotype: *ypt6*Δ strains are unable to complete autophagy at 37°C, yet the phenotype is reversible upon reincubation at 30°C.[8] By using protein degron technology[18] to construct a degradable version of Arl1, we temporarily induced loss of Arl1 in a *ypt6*Δ background and found that the cells now showed an autophagy defect at 30°C, suggesting that Arl1 and Ypt6 function reciprocally in autophagy.

The GTP-restricted allele of Arl1, *ARL1[Q72L]*, complements defects in membrane traffic,[9,10] while a nucleotide-free version of the protein, encoded by *ARL1 [N127I]* complements defects in K^+ homeostasis.[12,19] We therefore investigated which Arl1 alleles complemented the autophagy phenotype and found only wild type and the GTP-restricted allele, *ARL1[Q72L]* were able to do so, supporting the hypothesis that Arl1s role in the process is as a membrane traffic regulator. Interestingly, the *ARL1* allele, *ARL1[D151G]*, despite the fact that this allele appeared to extend lifespan in a *cdc28* mutant[14] was not able to complement the phenotypes we measured. However, similar to Arl1, the GTP-restricted allele of *YPT6, YPT6[Q69L]*, complemented the phenotype whereas a GDP-restricted allele, *YPT6[T24N]* did not.[8]

Arl1 and Ypt6 are necessary for the construction of the autophagosome, and are required for the anterograde traffic of the sole transmembrane protein known to be involved in autophagy, Atg9, to this structure. Moreover, the 2 GTPases are required for at least delivery of membrane components from the Golgi apparatus to the PAS, but whether they also are required for delivery of membrane components from other membranes (ER, mitochondria, etc.) remains an open question. Finally, based on previous data showing both Arl1 and Ypt6 interact with the Golgi-associated retrograde protein (GARP) complex (specifically, Arl1 binds to the Vps53 subunit[20] and Ypt6 binds to the Vps52 subunit[21] of the GARP complex) and that the GARP complex is necessary for some forms of autophagy,[22] we examined the colocalization of Arl1 and Ypt6 with GARP complex subunits Vps52 and Vps53 at the PAS upon induction of autophagy,[8] which resulted in the following model for the roles of these 2 small GTPases in macroautophagy (Fig. 1).

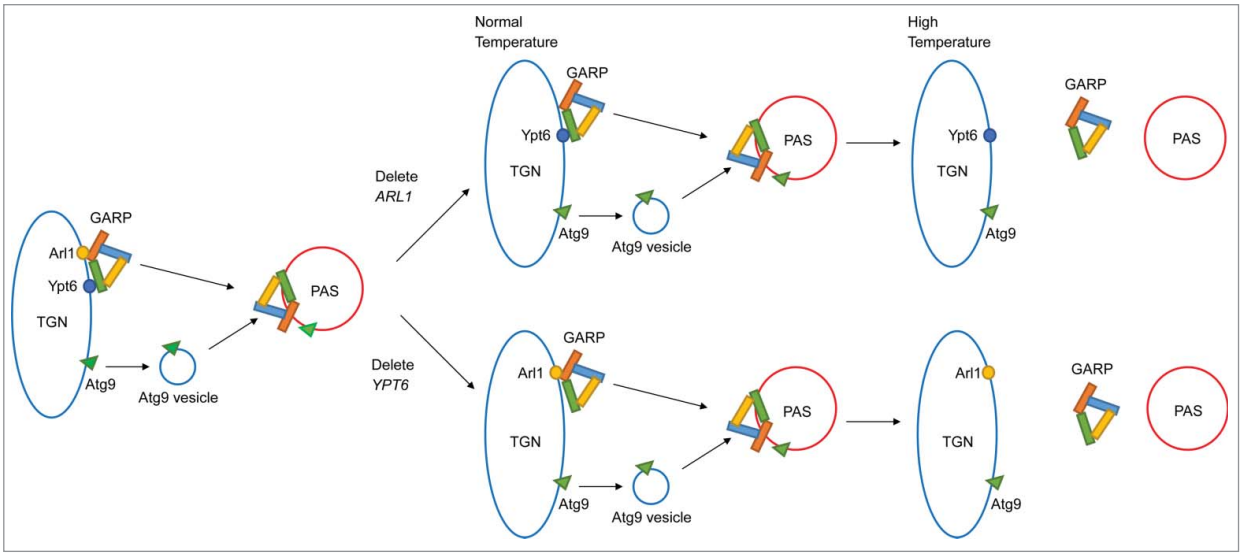

Figure 1. Current model for the reciprocal roles of Arl1 and Ypt6 in macroautophagy. Data shown in ref. 8 demonstrate that Arl1 and Ypt6 in *S. cerevisiae* function to deliver Atg9-containing vesicles from the Golgi apparatus to the growing phagophore at the phagophore assembly site (PAS) to make the autophagosome by virtue of their interactions with the Golgi-associated retromer complex (GARP). In mutants lacking either *ARL1* or *YPT6*, autophagy proceeds normally at the permissive temperature of 30°C because one of the 2 proteins is sufficient to bind to the GARP comples. However, in mutants lacking either of the genes, autophagy is inhibited at the restrictive temperature of 37°C presumably because the strength of the interaction with a single small GTPase is insufficient to retain GARP on the membrane at this temperature. A conditional mutant lacking both small GTPases is unable to perform autophagy at the permissive temperature.

Future directions

What is the complete set of small GTPase proteins required for macroautophagy?

There are several dozen small GTPases found in *S. cerevisiae*. The number found in multicellular eukaryotes is even larger, especially with respect to the Rab protein family (equivalent to the Ypt family in *S. cerevisiae*). No systematic study has been undertaken of all the GTPase proteins in even a simple unicellular organism like *S. cerevisiae*, although it is clear several members of the Arf/Arl/Sar and Ypt/Rab families are required for construction of the autophagosome and for fusion of the autophagosome with the vacuole.[4,23,24] Members of the Rac/Rho/Cdc42 family, proteins generally viewed as regulators of cell polarity and cytoskeletal function, also appear to have signaling roles in autophagy.[25,26] Interestingly, RhoA along with its downstream effector, ROCK1 appears to mediate switching between autophagy and apoptosis via control of Beclin-1 (the ortholog of Atg6 in *S. cerevisiae*) levels in mammalian cells.[24] Ras proteins appear to be involved in initiation of autophagy via regulation of TORC1.[27] In contrast, the GTPase complex made of Gtr1 and Gtr2 (equivalent to RagA and RagB in mammals) appears to stimulate TORC1.[28,29] At present, there is no evidence that Ran proteins, which regulate movement of molecules in and out of the nucleus via nuclear pores, have a role, but this question appears not to have been explored to date.

How does regulation of nucleotide binding on small GTPases affect macroautophagy?

The GTP-restricted versions of Arl1 and Ypt6 are required for autophagy.[8] Other GTPases in autophagy also function in the GTP-bound state; examples include Ypt1,[30,31] Ypt31/32,[32] and Ypt7,[33-35] suggesting that guanine nucleotide exchange factors (GEFs) are also important for autophagy. Indeed, the Mon1/Ccz1 GEF for Ypt7[33-35] and the Trs130 protein,[32] part of the complex that regulates Ypt31/32, have been shown to be necessary for autophagy. However, it may be challenging to determine which GEF is the relevant one for autophagy for a given small GTPase, including Arl1 and Ypt6, given that many small GTPases are turned on by several different GEFs and that many GEFs activate several different GTPases. For example, a network of GEFs and GTPases appear to work together for Arf and Arl proteins.[36,37] In addition, GEF proteins can be regulated spatially and temporally by the addition of protein subunits. As an example, the TRAPP complex which serves as a GEF for Ypt1 is found in 3 different forms, TRAPP I, which regulates traffic from the ER to the *cis*-Golgi; TRAPP II, which regulates intra-Golgi traffic; and TRAPP III, which is specific for autophagy share a number of subunits, but TRAPP II and TRAPP III have more subunits than TRAPP I.[30,31,38-41]

Recently, it has been demonstrated that Syt1, a GEF for Arl1, is phosphorylated upon induction of the unfolded protein response, resulting in increased activation of Arl1.[42] Similarly, the Rab12 GEF, DENND3 is phosphorylated by ULK1 (the ortholog of Atg1 in *S. cerevisiae*) which then promotes autophagy.[43,44] It is conceivable that other GEF post-translational modifications might be important for activation of small GTPases in their roles as modulators of autophagy.

By similar reasoning, GTPase activating proteins (GAPs) would also be expected to be important for regulation of autophagy, since they would be responsible for terminating the signals transmitted by GTPases in the GTP-bound state. This appears to be the case, at least for Rab proteins, where it has been shown that several Rab GAPs coordinate autophagy and "normal" functions of Rab proteins in the secretory pathway and endocytosis.[45-47] While the issue of networks of GAPs and GTPases may make this a challenging problem to investigate,[36,37] recent work has elucidated some of the details with respect to Rabs and RabGAPs in particular in different forms of autophagy, including in xenophagy, the process by which autophagy is induced in response to bacteria or viruses.[6]

Which effectors are required for macroautophagy?

Arl1 and Ypt6 appear to direct the GARP tethering complex to the growing autophagosome.[8] Other elements of the membrane traffic apparatus appear to be co-opted by the autophagy machinery in order to grow the autophagosome and then fuse the autophagosome with the vacuole/lysosome, including other tethering complexes, such as the HOPS complex downstream of Ypt7;[48] SNAREs;[49] coat proteins such as COPII, downstream of Ypt1;[50] and membrane deformation proteins such as Ivy1, an I-BAR protein downstream of Ypt7.[48] Likely other downstream effectors, including other modulators of membrane traffic will be revealed to have roles in autophagy.

Are small GTPases required for other forms of autophagy?

The preceding discussion focuses on macroautophagy, that induced by starvation. However, less is known about the roles of small GTPases in other forms of autophagy. We demonstrated that Arl1 and Ypt6 have modest roles in the cytosol-to-vacuole (CVT) pathway, a constitutive

process responsible for delivery of several enzymes to the vacuole in yeast.[8] However, we have not yet investigated whether these 2 GTPases have roles in other forms of autophagy, including mitophagy, induced to recycle defective mitochondria; pexophagy, for elimination of unwanted peroxisomes; ER-phagy, for elimination of excess ER; etc. These pathways, which have been shown to involve other small GTPases, will provide interesting avenues for future research into the roles of Arl1 and Ypt6 in cellular functions.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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