A unified nomenclature for yeast autophagy-related genes

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Letter to the Editor

A Unified Nomenclature for Yeast Autophagy-Related Genes

Perhaps the most striking advantage of working with certain yeast systems is the ability to use genetic screens that allow a relatively rapid identification of genes involved in various biological processes. Because of its smaller size, the *Saccharomyces cerevisiae* genome was the first eukaryotic genome to be sequenced. Subsequent sequencing of genomes from higher eukaryotes has revealed what had already been implicated from biochemical and molecular genetic studies performed over many years: homologs of yeast genes exist in other eukaryotes, and in many cases the corresponding gene products are orthologs that carry out similar functions (Reggiori and Klionsky, 2002). Accordingly, the analysis of genes and proteins in fungal cells has direct relevance for studies in other organisms.

Along these lines, fungal systems have proven to be extremely useful in the analysis of autophagy and autophagy-related processes (reviewed in Klionsky, 2003). Autophagy is a process in which portions of cytoplasm are sequestered by membrane(s), delivered to the lysosome-like vacuole, degraded, and recycled under stress conditions such as starvation. The sequestration process can occur either away from the vacuole (i.e., in the cytosol), in which case it is termed macroautophagy, or at the vacuole surface, termed microautophagy.

The identification of molecular components involved in macroautophagy has been carried out primarily in *S. cerevisiae*. In this organism, macroautophagy overlaps with a biosynthetic process termed the cytoplasm-to-vacuole targeting (Cvt) pathway. The Cvt pathway is an example of a specific type of autophagy; proteins that are destined to become resident vacuolar hydrolases are specifically packaged into cytosolic vesicles and delivered to the vacuole. There are also examples of specific degradative pathways. The best-characterized process is peroxisome degradation, or pexophagy. As with autophagy, peroxisome degradation can also occur by a micro- or macropexophagic process. In contrast to autophagy, pexophagy has been most thoroughly analyzed not in *S. cerevisiae* but in the methylotrophic yeasts *Hansenula polymorpha*, *Pichia pastoris*, and *P. methanolica*.

Due to the ease of genetic analyses in these and other yeast systems, several labs have carried out independent screens to identify mutants defective in the autophagy, Cvt, and pexophagy pathways. These studies have led to a range of names for genes involved in these processes, including: *APG*, *aut*o*p*hag*y* (Tsukada and Ohsumi, 1993); *AUT*, *aut*ophagy (Thumm et al., 1994); *CVT*, *c*ytoplasm-to-*v*acuole *t*argeting (Harding et al., 1995, 1996); *GSA*, *g*lucose-induced *s*elective *a*utophagy (Yuan et al., 1997); *PAG*, *p*eroxisome degradation via *a*utopha*g*y (Sakai et al., 1998); *PAZ*, *p*exophagy *z*eocin-resistant (Mukaiyama et al., 2002); and *PDD*, *p*eroxisome *d*egradation-*d*eficient (Titorenko et al., 1995).

The large number of names associated with these autophagy-related genes has added confusion to the field, and make it quite intimidating for researchers in other fields, or even for autophagy researchers in non-yeast systems, to keep track of the various gene products. Accordingly, following discussions at the first Gordon Research Conference on "Autophagy in Stress, Development, and Disease," the different labs working on these genes have recently decided to adopt a unified gene and protein nomenclature (Table 1). The new gene and protein names will be *ATG* and Atg, respectively, which stand for "*aut*opha*g*y-related." For simplicity, genes in *S. cerevisiae* are typically not denoted with a genus and species prefix. When referring to other yeasts, it is appropriate to use a capital followed by a lower case letter to designate the genus and species, respectively (e.g., *PpATG1* for the *Pichia pastoris* homolog of the *S. cerevisiae ATG1* gene, or PpAtg1 for the corresponding protein). For clarity, when comparing different organisms, however, it may be appropriate to use the "*Sc*" designation to denote *S. cerevisiae*.

For convenience, additional genes involved in autophagy-related processes are included in Table 2. These genes have been previously identified and the standard names as indicated in the *Saccharomyces* Genome Database will be used.

We consider it a notable feat to agree on a nomenclature that spans at least three genera and four species. There are putative homologs of autophagy genes in all eukaryotic organisms where genomic sequence information is available. In only a few cases, however, have analyses been carried out to demonstrate that the corresponding gene products are involved in autophagy (Table 3). For simplicity, we hope that researchers using higher eukaryotic systems will adopt the nomenclature presented in this paper. To avoid confusion in the yeast field, we urge authors of papers describing new autophagy-related genes to contact one of the authors of this paper prior to publication to avoid duplication when numbering new genes.

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Table 1. Description of Autophagy-Related Genes

Gene Designation								
Current	Former							
ATG	*APG*	*AUT*	*CVT*	*GSA*	*PAZ*	*PDD*	Reference	Protein Characteristics
1	1	3	10	10	1	7	Matsuura et al., 1997; Straub et al., 1997; Komduur et al., 2003; Mukaiyama et al., 2002; Harding et al., 1995; Stromhaug et al., 2001	Protein kinase
2	2	8	—	11	7	—	Shintani et al., 2001; Wang et al., 2001a; Barth and Thumm, 2001; Mukaiyama et al., 2004; Stromhaug et al., 2001	Peripheral membrane interacts with protein Atg9
3	3	1	—	20	—	—	Schlumpberger et al., 1997; Ichimura et al., 2000; Habibzadegah-Tari and Dunn, 2003	E2-like enzyme conjugates Atg8 to phosphatidylethanolamine (PE)
4	4	2	—	—	8	—	Lang et al., 1998; Kirisako et al., 2000; Mukaiyama et al., 2004	Cysteine protease; cleaves C-terminal extension or PE from Atg8
5	5	—	—	—	—	—	Kametaka et al., 1996	Conjugated to Atg12 through internal lysine
(6)[a]	6	—	—	—	—	—	Kametaka et al., 1998; Kihara et al., 2001	Component of PtdIns 3-kinase complexes I and II
7	7	—	2	7	12	—	Kim et al., 1999; Yuan et al., 1999; Tanida et al., 1999; Mukaiyama et al., 2004	E1-like enzyme activates Atg8 and Atg12
8	8	7	5	—	2	—	Lang et al., 1998; Kirisako et al., 2000; Harding et al., 1995; Mukaiyama et al., 2002	Ubiquitin-like protein conju gated to PE via C-terminal glycine
9	9	9	7	14	9	—	Noda et al., 2000; Lang et al., 2000; Mukaiyama et al., 2002; Stromhaug et al., 2001	Integral membrane protein
10	10	—	—	—	—	—	Shintani et al., 1999	E2-like enzyme; conjugates Atg12 to Atg5
11	—	—	9	9	6	18	Kim et al., 2001; Mukaiyama et al., 2002	Specific component involved in cargo recognition
12	12	—	—	—	—	—	Mizushima et al., 1998a	Ubiquitin-like protein; conjugated to Atg5 via C-terminal glycine
13	13	—	—	—	—	—	Funakoshi et al., 1997; Scott et al., 2000	Modifier of Atg1 activity; hyperphosphorylated in rich media
14	14	—	12	—	—	—	Kametaka et al., 1998; Kihara et al., 2001	Component of PtdIns 3-kinase complex I
15	—	5	17	—	—	—	Epple et al., 2001; Teter et al., 2001	Putative lipase required for breakdown of intravacuolar vesicles
16	16	—	11	—	3	—	Mizushima et al., 1999; Mukaiyama et al., 2002	Component of Atg12-Atg5 complex
17	17	—	—	—	—	—	Kamada et al., 2000	Modifier of Atg1 activity
18	—	10	18	12	—	—	Barth et al., 2001; Guan et al., 2001	Peripheral membrane protein; required for localization of Atg2
19	—	—	19	—	—	—	Scott et al., 2001; Leber et al., 2001	Cargo receptor for the Cvt pathway
20	—	—	20	—	—	—	Nice et al., 2002	PX domain protein needed for the Cvt pathway
21	—	—[b]	21	—	—	—	Barth et al., 2002	Specific to the Cvt pathway
22	—	4	—	—	—	—	Suriapranata et al., 2000	Integral membrane protein; involved in autophagic body breakdown
23	—	—[c]	23	—	—	—	Tucker et al., 2003	Needed for Cvt vesicle completion
(24)[d]	—	—	13	—	16	—	Nice et al., 2002; Y. Ano and Y.S., unpublished	Sorting nexin; PX domain-containing protein involved in the Cvt pathway and pexophagy
25	—	—	—	—	—	4	I.L. Monastyrska, J.A.K.W. Kiel, and M.V., unpublished	Coiled-coil protein involved in macropexophagy
26[e]	—	—	—	—	4	—	Mukaiyama et al., 2002; Oku et al., 2003; Stasyk et al., 2003	UDP-glucose:sterol glucosyltransferase-containing GRAM domain
27[f]	—	—	24	—	—	—	Wurmser and Emr, 2002	PtdIns(3)P binding protein required for the Cvt pathway

[a] The standard name for this gene is *VPS30*.
[b] This gene was originally named *MAI1*.
[c] This gene was also named *MAI2*.
[d] The standard name for this gene is *SNX4*.
[e] This gene was originally named *UGT51*.
[f] This gene was originally named *ETF1*.

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Table 2. Genes that Are Required for Autophagy but Also Function in Other Pathways

Gene	Alternative Designation						Reference	Protein Characteristics
	APG	*AUT*	*CVT*	*GSA*	*PAZ*	*PDD*		
ACS1	—	—	—	—	—	—	Kulachkovsky et al., 1997	Acetyl CoA synthase
ACS2	—	—	—	—	—	—	Kulachkovsky et al., 1997	Acetyl CoA synthase
ACS3	—	—	—	—	—	—	Kulachkovsky et al., 1997	
CCZ1	—	11	16	—	—	—	Wang et al., 2002; Meiling-Wesse et al., 2002a; Kucharczyk et al., 2001	Forms complex with Mon1; involved in fusion with the vacuole
GCN1	—	—	—	—	10	—	Mukaiyama et al., 2002	Regulates translation elongation
GCN2	—	—	—	—	11	—	Mukaiyama et al., 2002	Protein kinase; regulates translation initiation (eIF2α kinase)
GCN3	—	—	—	—	5	—	Mukaiyama et al., 2002	Translation initiation factor (eIF2B)
GCN4	—	—	—	—	19	—	Habibzadegah-Tari and Dunn, 2003	Transcriptional activator
ICL1	—	—	—	—	—	—	Kulachkovsky et al., 1997	Isocitrate lyase
MON1	—	12	—	—	—	—	Wang et al., 2002; Meiling-Wesse et al., 2002b	Forms complex with Ccz1; involved in fusion with the vacuole
PEP3[a]	—	—	—	—	—	—	Sato et al., 2000	Part of class C-Vps/HOPS complex required for fusion with the vacuole
PEP4	—	—	—	15	14	—	Takeshige et al., 1992; Habibzadegah-Tari and Dunn, 2003	Vacuolar proteinase A; involved in activation of Prb1
PEP5[b]	—	—	—	—	—	—	Sato et al., 2000	Zn finger protein; part of class C-Vps/HOPS complex required for fusion with the vacuole
PEX3	—	—	—	—	—	—	Bellu et al., 2002	Protein required for peroxisome biogenesis
PEX14	—	—	—	—	—	—	Bellu et al., 2001a	Protein required for peroxisome biogenesis
PFK1	—	—	—	1	—	—	Yuan et al., 1997	α subunit of PFK
PHO85	—	—	—	—	—	—	Wang et al., 2001b	Cyclin-dependent protein kinase; negative regulator
PRB1	—	—	1	—	—	—	Takeshige et al., 1992	Vacuolar proteinase B; involved in breakdown of intravacuolar vesicles
SEC12	—	—	—	—	—	—	Hamasaki et al., 2003	Guanine nucleotide exchange factor for Sar1
SEC24	—	—	—	—	—	—	Hamasaki et al., 2003	Component of the COPII vesicle coat
SNF1	—	—	—	—	—	—	Wang et al., 2001b	AMP-activated protein kinase; positive regulator
TLG2	—	—	—	—	—	—	Abeliovich et al., 1999	t-SNARE of the late Golgi involved in the Cvt pathway
TOR1/2	—	—	—	—	—	—	Noda and Ohsumi, 1998; Kamada et al., 2000	Protein kinase; negative regulator
TUP1	—	—	—	—	—	2	Titorenko et al., 1995; Bellu et al., 2001b	General repressor of transcription
VAC8	—	—	—	—	—	—	Wang et al., 1998; Scott et al., 2000; Roberts et al., 2003	Armadillo repeat protein involved in homotypic vacuole fusion, the Cvt pathway, and PMN
VAM3	—	—	—	—	—	—	Darsow et al., 1997	Vacuolar t-SNARE
VAM6	—	—	4	—	—	—	Wada et al., 1992; Price et al., 2000; Wurmser et al., 2000	GEF for Ypt7; Part of class C-Vps/HOPS complex required for fusion with the vacuole
VAM7	—	—	—	—	—	—	Sato et al., 1998	SNAP-25 homolog
VPS15	—	—	—	19	13	19	Kihara et al., 2001; Stasyk et al., 1999; Habibzadegah-Tari and Dunn, 2003	Protein kinase activates Vps34
VPS16	—	—	15	—	—	—	Sato et al., 2000	Part of class C-Vps/HOPS complex required for fusion with the vacuole

(continued)

Table 2. Continued

Gene	Alternative Designation						Reference	Protein Characteristics
	APG	*AUT*	*CVT*	*GSA*	*PAZ*	*PDD*		
VPS33	—	—	—	—	—	—	Sato et al., 2000	Part of class C-Vps/HOPS complex required for fusion with the vacuole
VPS34	—	—	—	—	—	1	Kihara et al., 2001; Kiel et al., 1999	Phosphatidylinositol 3-kinase
VPS41	—	—	8	—	—	—	Wurmser et al., 2000	Interacts with Vam6; part of class C-Vps/HOPS complex required for fusion with the vacuole
VPS45	—	—	—	—	—	—	Abeliovich et al., 1999	Member of Sec1 family; required for the Cvt pathway
VPS51	—	—	22	—	—	—	Reggiori et al., 2003	Forms a complex with the VFT proteins
VPS52	—	—	—	—	—	—	Reggiori et al., 2003	Component of the VFT complex composed of Vps52, Vps53, and Vps54; involved in retrieval from the endosome to the Golgi complex
VPS53	—	—	—	—	—	—	Reggiori et al., 2003	Component of the VFT complex
VPS54	—	—	—	—	—	—	Reggiori et al., 2003	Component of the VFT complex
VTI1	—	—	—	—	—	—	Fischer von Mollard and Stevens, 1999	v-SNARE required for Cvt pathway
YKT6	—	—	—	—	—	—	Kweon et al., 2003	R-SNARE required for the Cvt pathway
YPT7	—	—	—	—	—	—	Wichmann et al., 1992	Rab GTPase; required for fusion with the vacuole

[a] This gene has also been named *VPS18*.
[b] This gene has also been named *VPS11*.

Table 3. Orthologs of Autophagy-Related Genes in Higher Eukaryotes[a]

ATG	Gene Designation							Reference
	At[b]	*Ce*	*Dd*	*Dm*	*Hs*	*Mm*	*Rn*	
1	—	*unc-51*	*DdAPG1*	—	—	—	—	Meléndez et al., 2003; G.P. Otto and R.H. Kessin, personal communication
3	—	—	—	*DrAUT1*	*hAPG3*	—	—	Juhasz et al., 2003; Tanida et al., 2002b
4	—	—	—	*APG4/AUT2*	—	—	—	Thumm and Kadowaki, 2001
5	—	—	*DdAPG5*	—	*hAPG5*	*APG5*	—	Mizushima et al., 2001; Otto et al., 2003; Mizushima et al., 1998b
6	—	*bec-1*	*DdAPG6*	—	*beclin 1*	—	—	Liang et al., 1999; Meléndez et al., 2003; G.P. Otto and R.H. Kessin, personal communication
7	*AtAPG7*	*M7.5*	*DdAPG7*	—	*HsGSA7* *hAP G7*	*mAPG7*	—	Doelling et al., 2002; Otto et al., 2003; Tanida et al., 2001; Yuan et al., 1999; Meléndez et al., 2003
8	—	*lgg-1*	*DdAPG8*	—	*MAP1LC3*[c]	*mAPG8*	*LC3*	He et al., 2003; Tanida et al., 2002c; Otto et al., 2003; Meléndez et al., 2003
9	*AtAPG9*	—	—	—	—	—	—	Hanaoka et al., 2002
10	—	—	—	—	—	*mAPG10*	—	Mizushima et al., 2002
12	—	—	*DdAPG12*	—	*hAPG12*	*APG12* *mAPG12*	—	Mizushima et al., 2001; Tanida et al., 2002a; Mizushima et al., 1998b; Otto et al., 2003
16	—	—	*TipD*	—	—	*APG16L*	—	Mizushima et al., 2003; G.P. Otto and R.H. Kessin, personal communication
18	—	*F41E6.13*	—	—	—	—	—	Meléndez et al., 2003

[a] Only genes that have been mutated and shown to function in autophagy or that have been shown to interact with other autophagy-related proteins in published papers have been included in this table.
[b] Abbreviations: *At*, *Arabidopsis thaliana*; *Ce*, *Caenorhabditis elegans*; *Dd*, *Dictyostelium discoideum*; *Dm*, *Drosophila melanogaster*; *Hs*, *Homo sapiens*; *Mm*, *Mus musculus*; *Rn*, *Rattus norvegicus*.
[c] There are three homologs of human MAP1LC3, designated A, B, and C.

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