which control petal, stamen, and carpel development are good candidates for regulation by a gradient of WUS because they are expressed in the floral meristem in a pattern that is slightly broader than that of *AG*. Furthermore, it is likely that the *SEP* genes, like *AG*, are involved in repression of *WUS* because the *sep1/2/3* triple mutant flowers are also indeterminate (Pelaz et al., 2000). Another good candidate for activation by *WUS* is the *FRUITFULL* (*FUL*) MADS-box gene, which is expressed in a domain that is slightly smaller than that of *AG* and whose expression persists in the meristem of *ag* mutant flowers (Mandel and Yanofsky, 1995). It will be interesting to see how many genes achieve their spatially restricted expression domains through activation by WUS.

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Self-Destruction in the Line of Duty

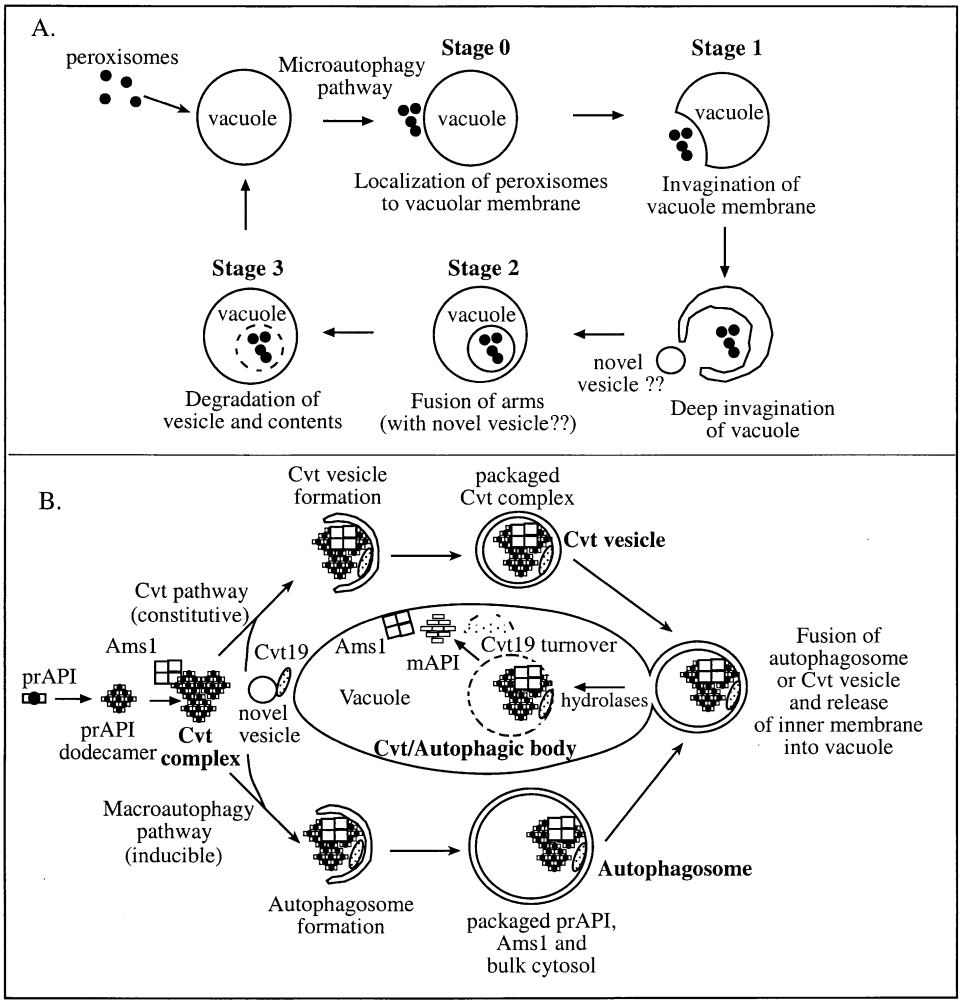
Three cellular processes, microautophagy, macroautophagy, and the cytoplasm-to-vacuole (Cvt) pathway, are involved in the cargo delivery from the cytosol to the vacuole or lysosome. Recent findings have identified Cvt19 at the receptor for specific cargo binding in the Cvt pathway.

The processing or turnover of cellular macromolecules in yeast vacuoles or their mammalian counterpart, the lysosomes, fulfills biosynthetic and recycling functions that are important for cell growth, survival, and development. These processing events depend on the activity of vacuolar or lysosomal hydrolases and require mechanisms for the delivery of cargoes (specific proteins, unnecessary organelles, or bulk cytosol) from the cytosol and the extracellular medium to the lumen of the lysosomes. Multiple pathways exist for the delivery of specific and nonspecific cargoes from the cytosol to the vacuole or lysosome (Klionsky and Ohsumi, 1999). Three of these routes (microautophagy, macroautophagy, and the Cvt pathway; see figure) exhibit substantial overlap and share many proteins whose functions are still being elucidated. Two recent papers (Leber et al., 2001; Scott et al., 2001) describe the characterization of an unusual membrane-bound receptor required for the delivery of proteins specifically to the Cvt pathway.

Delivery of Cargo to the Vacuole or Lysosome by the Autophagy and Cvt Pathways

There are two forms of autophagy, termed microautophagy and macroautophagy (Dunn, 1994). In the former, nonspecific bulk cytosol or specific but dispensable organelles are engulfed by invagination of the vacuolar membrane. The engulfing arms then fuse, resulting in the vacuolar delivery of the cargo wrapped in a single membrane derived from the invaginated vacuolar membrane (Sakai et al., 1998). In macroautophagy and the Cvt pathway, a double membrane of unknown origin wraps around the proteins, cytosol, or organelles to be degraded and fuses at its edges to create a dual-membrane vesicle surrounding the cargo. The outer membrane of these double-membrane vesicles, called autophagosomes or Cvt vesicles, respectively, fuses with the vacuolar membrane to deliver cargo surrounded by a single membrane into the vacuole (Klionsky and Ohsumi, 1999). In all three processes, the single membrane surrounding the cargo is then destroyed by vacuolar hydrolases and the enclosed contents are released into the vacuolar lumen for delivery, processing, or turnover (see figure).

In contrast to the autophagy modes, the Cvt pathway is biosynthetic rather than degradative and appears to be a mechanism for the delivery of oligomerized proteins into the vacuole lumen, where their functions are necessary. In *Saccharomyces cerevisiae*, the Cvt pathway selectively delivers enzymes, such as a precursor of aminopeptidase I (prAPI) and α-mannosidase (Ams1) to the vacuole. The Cvt pathway is distinct from macroautophagy in terms of its cargo selectivity, saturability, faster kinetics, constitutive nature, and the smaller size of the Cvt vesicles. However, many genes involved in this process (*CVT* genes) are shared with those necessary for macroautophagy (*APG/AUT* genes) and to a lesser extent with those needed for glucose-stimulated microautophagy (*GSA* genes) in *Pichia pastoris* (Yuan et al., 1999). Furthermore, proteins such as API that are normally routed via the Cvt pathway can find their way to the vacuole via macroautophagy under starvation conditions, which induce this process (Klionsky and Ohsumi, 1999). The specific degradation of organelles such as peroxisomes (called pexophagy) in *S. cerevisiae* also requires many of the same *CVT/APG/AUT* genes and may be a form of autophagy that targets specific cargo (Hutchins et al., 1999). This view is supported by the finding that specific peroxisome degradation in methylotrophic yeasts can occur both by macroautophagy and



Schematic Depiction of Steps in the Delivery of Cytosolic Proteins, Organelles, or Bulk Cytosol to the Vacuole by Microautophagy, the Cvt Pathway, or Macroautophagy

The involvement of a novel vesicle in fusion event(s) in microautophagy is speculative, but is suggested here to reconcile the involvement of several *APG/CVT/AUT* genes in microautophagy.

microautophagy, depending on the media that the cells are in (Tuttle and Dunn, 1995; Veenhuis et al., 1983).

Studies on the Cvt pathway in yeast have revealed that prAPI is synthesized in the cytosol, where it forms dodecamers. Many such dodecamers congregate in a membrane-bound assembly called the Cvt complex, which is then engulfed by a double membrane to form the Cvt vesicle described earlier. The papers referred to above (Leber et al., 2001; Scott et al., 2001) describe the characterization of a receptor, named Cvt19 by agreement between the two groups, to which API dodecamers bind prior to the formation of the Cvt complex. The discovery of this receptor explains how cargo selection and specificity are achieved in the Cvt pathway, in contrast to the nonselective cargo delivered by macroautophagy.

A Receptor for the Cvt Pathway

The *CVT19* gene was defined not by a screen for *cvt* mutants, but in a genome-wide, yeast two-hybrid analysis for API-interacting proteins (Uetz et al., 2000). Deletion of this ORF (YOL082w) of unknown function revealed that it is necessary for vacuolar transport of API (Leber et al., 2001; Scott et al., 2001) and Ams1 via the Cvt pathway (Scott et al., 2001) but not for the autophagic degradation of either bulk cytosol or peroxisomes. The gene encodes a predicted protein of 48 kDa that was localized to membranes of novel, mobile vesicular structures near the vacuole by both groups (Leber et al., 2001; Scott et al., 2001) and also to the cytosol (Leber et al., 2001). It is possible that the use of N- or C-terminal GFP fusions by the two groups is responsible for the difference of opinion regarding the cytosolic pool of Cvt19. Another protein, Cvt9/Gsa9, was localized to a similar vesicular structure near the vacuole, but no colocalization data are available for Cvt9 and Cvt19 (Leber et al., 2001).

Both groups find that Cvt19 interacts with prAPI and agree that this binding is enhanced by the presequence of prAPI, suggesting that Cvt19 serves as the membrane-bound receptor for the formation of the Cvt complex. The dependence of Cvt19 binding on the presequence makes sense because it is necessary for the vacuolar sorting of prAPI by the Cvt pathway. However, while one group finds that Cvt19 does not coimmunoprecipitate with mAPI (Scott et al., 2001), the other group

does detect interaction between the two proteins using the yeast two-hybrid system (Leber et al., 2001), raising a question about the binding of Cvt19 solely to the presequence of prAPI.

Supporting the premise that Cvt19 is the prAPI receptor is the finding that Cvt19 is degraded in the vacuole with similar kinetics as the processing of prAPI, and that its turnover is dependent on other components of the Cvt pathway and the vacuolar proteinase encoded by the *PEP4* gene (Scott et al., 2001). Cvt19 is also needed for the specific and rapid vacuolar delivery of API by macroautophagy under starvation conditions but not for the slower, nonspecific delivery of API to vacuoles (Leber et al., 2001).

One surprise is that unlike most receptors that act in multiple rounds of binding and release, Cvt19 is unorthodox in that it self-destructs in the vacuole while delivering API there. This seems like a costly price for specificity, but perhaps the inefficiency is mitigated by the fact that multiple dodecamers of prAPI (and also Ams1 oligomers) may be delivered to the vacuole by each Cvt19 molecule. Another unexpected result is that although there is genetic evidence for a role of Cvt19 in Ams1 delivery to the vacuole, no interaction was detected between Cvt19 and Ams1 (Scott et al., 2001). It is possible that the low abundance of Ams1 makes such an interaction difficult to detect, but an alternative possibility compatible with the genetic data and the absence of a presequence in Ams1 is that the Cvt complex, including Ams1, may interact with Cvt19 solely via prAPI. This point also raises the question of what other cargoes might need Cvt19 and the Cvt pathway for vacuolar delivery.

Since the Cvt pathway is constitutive in vegetative cells, do Cvt vesicles participate in a futile cycle of formation in the cytosol and degradation in the vacuole in the absence of cargo? Some light is shed on this problem by the finding that the vacuolar turnover of Cvt19 is API dependent (Scott et al., 2001), but the broader question remains in the absence of complete knowledge of all Cvt cargoes.

We are also left with some other unanswered questions. What protein and/or lipid confers upon Cvt19 its binding specificity for the punctate, vesicular structures near the vacuole? What is the nature and origin of these structures? Is the proximity of these structures to the vacuole reflective of their organelle of origin or of their final site of consumption at the vacuole? Somewhat surprisingly, even in the absence of Cvt19 multimeric prAPI associates with membranous structures, albeit less strongly than in wild-type cells, raising the possibility that some other protein and/or lipid functions with Cvt19 as either upstream- or co-receptors for prAPI (Scott et al., 2001). The rapid progress in this field promises that answers to these queries and perhaps a uniform gene nomenclature system will be forthcoming.

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Fas-Acting Memory

Genetic and behavioral analysis points to a role for fasciclin II in controlling odor memory and alcohol sensitivity in *Drosophila*.

Regulation of cell-adhesion molecules can bring about alterations in synaptic structure that are plausibly associated with long-term changes in memory. Surprisingly, some of these adhesion molecules are also implicated in immediate learning.

It is likely that forming new memories involves changes in the efficacy of individual synapses in specific neuronal circuits. Evidence from many systems implicates second-messenger systems in these synaptic changes. Current models envisage that short-term memories are stored as labile electrophysiological changes at synapses, whereas long-term memories are encoded as structural alterations at the same synapses. Many studies have indicated a role for cell-adhesion molecules in the long-term, morphological type of synaptic change (Martin and Kandel, 1996). However, the true picture may not be that simple. Studies with the *Drosophila* memory mutant *volado*, whose gene encodes an α-integrin subunit, demonstrated that cell-adhesion molecules can also be critical for short-term memories (Grotewiel et al., 1998). A recent paper in *Cell* extends this finding by implicating yet another *Drosophila* cell-adhesion molecule, fasciclin II (FasII), in short-term memory formation (Cheng et al., 2001).

Many *Drosophila* learning genes are highly expressed in the adult fly mushroom bodies (MBs)—brain structures that are necessary for olfactory learning (Zars, 2000). The Davis group has previously screened *Drosophila* P element enhancer-trap lines to find genes that are expressed at high levels in the MBs (see Cheng et