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**Title:**

HOPping to the vacuole: Autophagosome and late endosomes combine to control plant autophagosome degradation

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**Abstract**

In this issue of *Developmental Cell*, Jiang et al. (2024) report that the Arabidopsis HOPS tethering complex subunit VPS41 acts to catalyse the formation of a degradation pathway composed of a hybrid of autophagosomes and late endosomes.

**Main text:**

Autophagy is an essential intracellular degradation pathway in eukaryotes which involves the engulfment of cellular material into double-membrane structures called autophagosomes<sup>1</sup>. In plants autophagy is induced by a diverse array of abiotic and biotic stresses, including nutrient starvation, pathogens, and osmotic stress<sup>2</sup>. The general mechanisms for autophagosome formation in eukaryotes are largely conserved. Autophagosomes are formed through the assembly of a crescent-shaped isolation membrane, named the phagophore, which expands around cargo and subsequently closes. Following this, the autophagosomes fuse with the lytic vacuole. The mechanisms by which autophagosomes are transported to the vacuole and fuse with the tonoplast to deliver cargo for degradation is only beginning to be understood in plant cells. Here Jiang et al. provide substantial biochemical, genetic, and microscopic evidence that VPS41 facilitates a distinct autophagosome-to-vacuole fusion pathway that is induced upon a wide variety of stresses<sup>3</sup>.

In animals and yeast, the tethering and fusion of autophagosomes with the vacuole or lysosome requires the HOPS complex (tethering machinery), SNAREs (fusion machinery), and regulators such as the small GTPase Rab7. Whether key components mediated autophagosome fusion with the vacuole are evolutionarily conserved, or whether plant-specific mechanisms exist had not been thoroughly investigated. Notably, plants have an expansion of protein components implicated in vacuolar trafficking<sup>4</sup>, suggesting that they have evolved distinct vacuole-directed trafficking pathways facilitated by the specialisation of evolutionarily conserved trafficking machinery.

In this study, Jiang et al. investigated the role of the *Arabidopsis thaliana* HOPS complex subunit VPS41. VPS41 has been previously implicated in vacuole trafficking in plants<sup>5</sup>, and found to assemble into large ER-associated assemblies which resemble biomolecular condensates<sup>6</sup>. Consequently, the authors proposed that VPS41 carries out plant-specific functions related to vacuole trafficking<sup>6</sup>. Using live-cell imaging and immunogold transmission electron microscopy (TEM) experiments, Jiang et al. discovered that, following autophagy induction, VPS41 converts from condensates to ring-like structures which enclose a subpopulation of autophagy compartments<sup>3</sup> (labelled with the autophagy-related protein ATG8, **Figure 1**). They named these structures VPS41-associated phagic vacuoles (VAPVs).

What are VAPVs and how do they form? The authors found that disrupting the formation of VAPVs blocks the transport and fusion of autophagosomes to the vacuole thus reducing autophagy degradation and impairing plant survival upon carbon starvation. They thus propose that VAPVs are matured forms of autophagosome, en route to the vacuole. VAPVs were found to be independent of other endomembrane compartments besides partially co-localizing with late endosomes (LEs)/multi vesicular bodies (MVBs). VPS41 was observed on the membrane of developing phagophores, and mutants impaired in autophagosome formation showed reduced number of VAPVs, suggesting that the formation of VAPVs can occur concomitantly with autophagosome formation. Reciprocally, mutants altered in VAPVs formation accumulate abnormal autophagy compartments, suggesting that VAPVs contribute to the structure of autophagosomes. Using TEM analyses, the authors could capture images of intermediate compartments in the formation of VAPVs. These images lead them to propose that LEs fuse with the developing phagophore before closure (**Figure 1**). This would suggest that the content of LEs fills the lumen of developing phagophore during the fusion process, which later becomes the lumen between the inner and outer membrane of VAPVs. How the autophagy machinery coordinate with the formation of VAPVs, in a compartment that the authors found acidic and degradative in nature, remains intriguing and should be the focus of future exciting studies.

Jiang et al. also identified key molecular machinery required for the VAPV autophagy pathway. This includes the ARF-like GTPases ARLA1 (a homolog of human ARL8b) which physically interacts with VPS41 and is required for VAPV formation, thereby acting as an upstream regulator. Furthermore, VAPV formation and fusion with the vacuole involves the Q-SNAREs SYP22 and VTI11 (ZIG1), which form a SNARE complex and were previously shown to interact with the VPS41 and HOPS complex subunits<sup>5,7</sup>. Whether SNAREs mediate direct recruitment of HOPS to the VAPV or intermediate structures remains unclear. Surprisingly, VAPV were still formed in a Rab7 mutant which is impaired in Rab5-to-Rab7 mediated trafficking, a prominent vacuole trafficking pathway in eukaryotes. This finding demonstrates key evolutionary differences in autophagosome-vacuole fusion in plants, with plants not requiring Rab7 for HOPS complex activation vacuolar fusion as in animals or yeast.

By unravelling a critical step in autophagosome/vacuole transport, this beautiful work by Jiang et al. opens key questions into the mechanism of the plant autophagy pathway. A major finding of this study is that VAPVs are triggered by a diverse range of autophagy-inducing stresses, surround a variety of autophagosome populations (i.e. labelled by distinct ATG8 proteins), and are observed in multiple cell/tissue types, implying that this autophagosome transport pathway is an integral part of autophagy in plants. However, only a portion of autophagosomes are enclosed by VPS41, suggesting that these VAPVs are specialised mature forms of autophagosomes which exist alongside traditional autophagosomes.

Further questions resulting from this work thus include: how and why do autophagosomes transition to VAPVs? What are the molecular determinants which specify which autophagosomes mature into VAPVs, and how do they cooperate with the autophagy machinery to coordinate VAPV and autophagosome formation? Since previous work from the authors found that VPS41 condensates are much less abundant in the root elongation zone and leaves compared to the root meristem<sup>6</sup>, are VAPVs differentially formed and controlled in specific tissues or organs? Addressing the prevalence of VAPVs as mature forms of autophagosomes, in regard to other types of amphisomes (such as CFS1-regulated compartments<sup>8</sup>) in a cell type, tissue and developmental context will be of great interest to expand our understanding of the structure and function of these compartments. Finally, future work could address the function of VPS41 condensates in autophagosome formation and maturation, for example to test whether the condensates act as protein storage hubs in preparation for the onset of autophagy.

### Figure legend :

**Figure 1:** Overview of VAPV formation during autophagosome biogenesis and fusion with the vacuole in plants. Upon autophagy induction VPS41 converts from condensates to ring-like structures enclosing autophagy compartments labelled by the autophagy-related protein ATG8. Further fusion with late endosomes enables the formation of VPS41-associated phagic vacuoles (VAPV), a matured form of autophagosomes en route to the vacuole.

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## Competing interests

The authors declare no competing interests

