AUTOPHAGY

Acetylation rules VPS34

Mol. Cell **67**, 907–921 (2017)

The class III phosphoinositide 3-kinase VPS34 generates phosphatidylinositol 3-phosphate (PI3P) to regulate vesicular trafficking and autophagy. VPS34 interacts with regulatory proteins in complexes during autophagy induction, yet VPS34 activation is not fully understood. Liu and colleagues report that VPS34 is regulated by p300 and p300-mediated activation of VPS34 can be used, not only during starvation-induced autophagy, but also during non-canonical autophagy induction, independent of upstream kinases.

Using bioinformatics followed by acetylation assays and experiments using histone deacetylase family inhibitors, the authors showed that VPS34 is regulated by p300-mediated acetylation. Mutant analyses indicated that acetylation suppresses VPS34 lipid kinase activity by decreasing its affinity for its substrate PI. Testing VPS34 interaction with its regulator Beclin1 showed that acetylation hindered VPS34–Beclin1 complex formation. The authors showed that p300-mediated VPS34 acetylation functions in response to starvation as well as in non-canonical autophagy.

These data uncover a previously unknown pathway for VPS34 activation and indicate that p300 acetylation controls VPS34 kinase activity and complex formation with its regulatory proteins. Whether acetylation regulates other VPS34-dependent membrane processes remains to be determined. *CK*

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AUTOPHAGY

Liver autophagy's sweet side

Genes Dev. **31**, 1655–1665 (2017)

In the liver, autophagy is thought to maintain systemic nutrient and energy balance upon starvation. Whereas glucagon is known to induce autophagy, the physiological function and mechanisms of glucagon-related autophagy are not well defined. O-linked β-*N*-acetylglucosamine (O-GlnNAc) signalling is critical to liver metabolism, and O-GlcNAc has been proposed to function as a nutrient sensor. Yang and colleagues find that O-GlcNAc transferase (OGT) is required for liver autophagy upon glucagon stimulation and in response to starvation.

Experiments with mice deficient for hepatic Atg5 showed Atg5-mediated autophagy in the liver was required for glucagon to induce the starvation response. Treatment with O-GlcNAcase inhibitor suggested that OGT promoted autophagy. Liver-specific OGT knockout indicated that hepatic OGT mediated metabolic adaptations to starvation. Further studies suggested calcium/calmodulin-dependent kinase II (CaMKII) phosphorylated OGT to promote autophagy, and this was confirmed in CAMKII liver-specific knockout mice. The authors then showed that O-GlcNAcylation controls autophagy by modulating Ulk1 phosphorylation and activity.

This study delineates that glucagon induces calcium signalling, leading to CAMKII phosphorylation of OGT, which promotes Ulk1 O-GlcNAcylation and autophagy, linking liver autophagy to systemic nutrient homeostasis. *CK*

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AUTOPHAGY

Splitting up for mitophagy

J. Cell Biol. **216**, 3231–3247 (2017)

Protein aggregation within the mitochondrial matrix promotes Parkin recruitment and PINK1–Parkin-dependent mitophagy. Yet how Parkin mediates selective autophagic elimination of misfolded proteins localized to mitochondria, and the role of mitochondrial fission in mitophagy, have remained unclear.

Youle and colleagues report that PINK1 recruits Parkin to focal sites on mitochondria harbouring misfolded protein aggregates, and that mitochondrial fission protects undamaged mitochondria from elimination.

Using a system to visualize misfolded aggregates of mitochondrial-localized mutant ornithine transcarbamylase (ΔOTC), the authors showed that PINK1 recruited cytosolic Parkin to focal spots on mitochondria that were proximal to ΔOTC. Induction of mitochondrial misfolding also caused PINK1-dependent Parkin recruitment to polarized mitochondrial subdomains. Autophagy receptors and LC3 were recruited to Parkin foci in ΔOTC-expressing cells and co-localized with ΔOTC in a PINK1-dependent manner. The authors found that mitochondrial fission factor Drp1 recruitment to Parkin foci triggered fission of mitochondrial subdomains harbouring ΔOTC, but not ΔOTC clearance. Rather, Drp1 loss increased Parkin recruitment and mitophagy and decreased the selectivity of mitophagy.

These findings suggest that mitochondrial fission, rather than promoting unchecked mitophagy, restricts PINK1–Parkin activity to mitochondrial subdomains harbouring misfolded aggregates, sparing healthy mitochondria from removal. *CK*

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AUTOPHAGY

A STING in ER-phagy

Cell **171**, 809–823 (2017)

Cyclic-di-adenosine monophosphate (c-di-AMP) is a bacterial second messenger that induces the interferon response through the innate sensor stimulator of interferon genes (STING). Innate immune system discrimination between self and non-self depends on pathogen-associated molecular pattern (PAMP) recognition. Microorganisms signal viability through vita-PAMPs present in live, but not dead, microorganisms. However vita-PAMPs and the responses they induce are not well defined.

Blander and colleagues identify c-di-AMP as a vita-PAMP that induces STING-dependent endoplasmic reticulum (ER) stress to protect mice against bacterial infection through inactivation of mTOR and induction of autophagy.

The authors studied phagocyte responses to avirulent Gram-positive *Listeria innocua* and found that live, but not dead bacteria induced autophagy by inactivating mTORC1. Live bacteria elicited an ER stress response critical for defence against infection, and autophagy inhibition sustained ER stress and induced cell death following infection. Fractionation experiments indicated ER-stress-mediated autophagy sequesters stressed ER membranes. A quantitative mass spectrometry approach identified STING as enriched in autophagosomes during the bacterial response. The authors then uncovered how STING senses c-di-AMP as a vita-PAMP to induce autophagy and interferon response.

This elegant work links immune signalling and autophagy in a mechanism that allows cells to respond to threats and survive infection by maintaining homeostasis. *CK*

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