



AUTOPHAGY

Kinase ups and downs

The class III phosphoinositide 3-kinase vacuolar protein sorting 34 (VPS34) phosphorylates phosphatidylinositol (PtdIns) to produce PtdIns-3-phosphate (PtdIns3P), which is essential for autophagy. Previous studies suggest that autophagy is inhibited during mitosis. Furuya *et al.* now show that the mitotic kinase cyclin-dependent kinase 1 (CDK1) and a second kinase, CDK5, phosphorylate and inactivate VPS34 in mitotic cells, resulting in reduced autophagy.

The authors observed a decrease in the number of autophagosomes

“ VPS34 phosphorylation negatively regulates autophagy. ”

(subcellular structures that form during autophagy) in human cells during mitosis in parallel with a reduction in PtdIns3P, and postulated that CDK1 might negatively regulate VPS34 to cause this outcome. Indeed, CDK1 phosphorylates wild-type VPS34, and a VPS34 mutation at Thr159 reduces the level of CDK1-mediated VPS34 phosphorylation, indicating that CDK1 phosphorylates VPS34 on Thr159.

But, does CDK1 phosphorylate VPS34 on Thr159 during mitosis? The authors synchronized cells in mitosis and found that phosphorylation of VPS34 on Thr159 was increased during mitosis. This increase was blocked when cells were also treated with CDK1 inhibitors. CDK5, which does not play a part in the cell cycle but phosphorylates certain CDK1 substrates, can also phosphorylate VPS34 on Thr159 (as well as Thr668), both *in vitro* and *in vivo*.

So, what is the biological significance of VPS34 phosphorylation on Thr159? The kinase activity of VPS34

depends on its interaction with regulatory proteins, including beclin 1. Phosphorylation of VPS34 on Thr159 by CDK5 or CDK1 reduces the lipid kinase activity of VPS34 under starvation (which induces autophagy), as judged by a reduction in the level of PtdIns3P in cells, and VPS34–beclin 1 interactions. Expression of VPS34 that cannot be phosphorylated on Thr159 increases the level of autophagy under certain conditions, further suggesting that VPS34 phosphorylation negatively regulates autophagy.

Thus, a decrease in the level of autophagy during mitosis might be due to an increase in CDK1-mediated VPS34 phosphorylation and a subsequent decrease in the levels of VPS34 kinase activity and PtdIns3P.

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ORIGINAL RESEARCH PAPER Furuya, T. *et al.* Negative regulation of Vps34 by Cdk mediated phosphorylation. *Mol. Cell* **38**, 500–511 (2010)

FURTHER READING Vanhaesebroeck, B. *et al.* The emerging mechanisms of isoform-specific PI3K signalling. *Nature Rev. Mol. Cell Biol.* **11**, 329–341 (2010)