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AUTOPHAGY

# Breaking and exiting

> “…autophagy contributes to the establishment of senescence.”

How cells switch from a proliferative state to a senescent state in response to cellular stress is not fully understood. Young *et al.* now suggest an intriguing new role for autophagy — a process that involves the lysosomal breakdown of cytoplasmic components — in the establishment of senescence.

To determine whether autophagy is involved in oncogene-induced senescence (OIS), the authors assessed the level of the autophagy marker LC3-II during senescence induced by the Ras oncoprotein. LC3-II was upregulated in senescent cells, indicating the accumulation of autophagosomes. Cells undergoing Ras-induced senescence also showed an increase in the degradation of long-lived proteins, which is further suggestive of autophagy.


PHOTODISC

Mammalian target of rapamycin (mTOR) is a Ser/Thr kinase that forms two distinct complexes, mTORC1 and mTORC2, that negatively regulate autophagy. mTORC2 negatively regulates the transcription factor FOXO3A by inducing its phosphorylation through AKT. FOXO3A activates a subset of autophagy-related (*ATG*) genes. Microarray analysis revealed a decrease in FOXO3A phosphorylation, which is indicative of an increase in its transcriptional activity, in parallel with increased levels of *ATG* transcripts during the transition to OIS. Many lysosomal genes were also upregulated, suggesting the coordinated regulation of *ATG* and lysosomal genes, which is consistent with the possibility of autophagy during OIS. In a separate experiment, overexpression of *ULK3* (a potential human homologue of yeast *ATG1*, which regulates autophagy under the control of mTORC1) was sufficient to induce autophagy and senescence. Thus, both the mTORC2–FOXO3A and mTORC1–ULK3 pathways seem to be involved in the induction of autophagy in senescence.

The transition to senescence is accompanied by increased secretion of the pro-senescent cytokines interleukin 6 (IL-6) and IL-8. Rapid protein turnover, which involves autophagy coupled with active protein synthesis, could facilitate this process. Indeed, increased amino acid uptake was observed in Ras-induced senescent cells. Strikingly, depletion of the *ATG5* or *ATG7* transcripts, which are essential for autophagy, delayed IL-6 and IL-8 production. This highlights the functional relevance of autophagy in establishing senescence. The requirement of autophagy in senescence was further enforced by the fact that *ATG5* and *ATG7* depletion also increased the ability of cells to bypass senescence in a colony formation assay. These data suggest that autophagy contributes to the establishment of senescence.

Finally, the authors tested the relevance of autophagy during OIS *in vivo*. Markers of autophagy and senescence colocalized in murine papillomas containing active Ras, and were more prominent in transition areas between proliferative and non-proliferative regions. So, autophagy seems to have a crucial role in the transition phase of senescence establishment *in vitro*, and these important cellular processes might also be linked *in vivo*.

*Katharine H. Wrighton*

**ORIGINAL RESEARCH PAPER** Young, A. R. J. *et al.* Autophagy mediates the mitotic senescence transition. *Genes Dev.* 11 March 2009 (doi:10.1101/gad.519709)

**FURTHER READING** Klionsky, D. J. Autophagy: from phenomenology to molecular understanding in less than a decade. *Nature Rev. Mol. Cell Biol.* **8**, 931–937 (2007)



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