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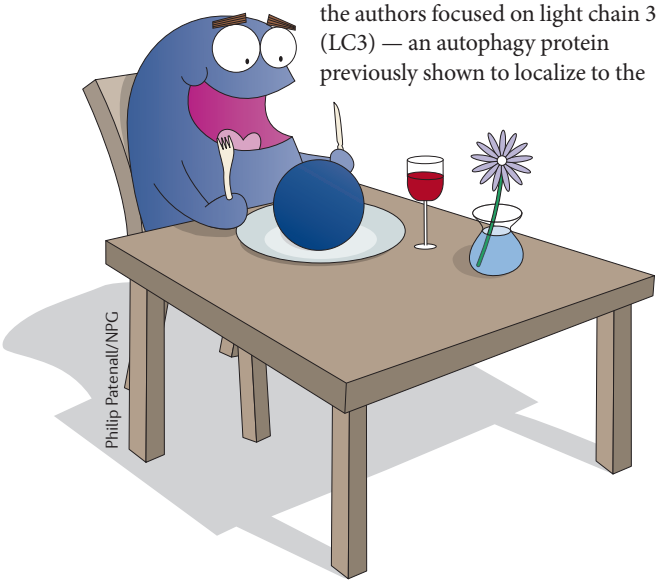
AUTOPHAGY

Nuclear autophagy in tumour suppression

> oncogenic insults induce nuclear autophagy, leading to degradation of lamin B1



Autophagy is a process of cellular self-consumption that has been associated with various human diseases, including cancer. The majority of studies on autophagy to date have focused on the degradation of cytoplasmic components with little attention to the nucleus. Thus, the mechanisms and roles of nuclear autophagy have so far remained elusive. Dou *et al.* now provide evidence that autophagy of nuclear components can serve as a potential tumour suppressive mechanism.

To investigate nuclear autophagy, the authors focused on light chain 3 (LC3) — an autophagy protein previously shown to localize to the nucleus. They found that in cultured cell lines, LC3 strongly interacted with lamin B1 — an important component of the nuclear lamina (a protein meshwork underlying the nuclear membrane).

Previous studies demonstrated that lamin B1, but not other lamin family members, is downregulated in primary cells upon exposure to oncogenic stimuli. Oncogenic challenge has also been associated with upregulation of autophagy, as well as stable withdrawal from the cell cycle, resulting in cellular senescence — a mechanism that probably prevents cells from transformation and safeguards against tumorigenesis. This collectively prompted Dou *et al.* to investigate the links between lamin B1, autophagy and cellular senescence.

The authors found that oncogenic stimuli induced substantial nuclear abnormalities in primary cells, including formation of spherical membranous protrusions (blebs) at the nuclear membrane, indicative of nuclear autophagy. These nuclear changes were further associated with the redistribution of lamin B1 from the nuclear lamina to cytoplasmic vesicles, which were eventually targeted to the lysosome, indicating lysosomal degradation of lamin B1.

The cytosolic release and subsequent degradation of lamin B1 depended on the induction of autophagy and on the interaction between LC3 and lamin B1. Notably, downregulation of lamin B1 protein occurred specifically in response to oncogenic insults and was not observed when autophagy was induced with alternative methods. This suggested that oncogenic stimuli are capable of triggering a specific autophagy response, which is translated to the nucleus via nuclear autophagy proteins such as LC3, leading to the release of lamin B1 to the cytoplasm and its lysosomal degradation. Further experiments revealed that the perturbation of the degradation of lamin B1 was associated with a delay in the induction of cellular senescence triggered by an oncogenic challenge.

Altogether, this study provides evidence that oncogenic insults induce nuclear autophagy, leading to degradation of lamin B1 (and possibly also of other nuclear components). This mechanism appears to be important for timely acquisition of cellular senescence upon oncogenic challenge and thus may play a part in tumour suppression. It would be interesting to investigate exactly how this selective degradation of the nuclear lamina is mechanistically achieved and how it signals to regulate senescence.

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ORIGINAL RESEARCH PAPER Dou, Z. *et al.* Autophagy mediates degradation of nuclear lamina. *Nature* http://dx.doi.org/10.1038/nature15548 (2015)