DOI:
10.1038/nrm2214

URLs

BECN1
http://www.ncbi.nlm.nih.gov/sites/entrez?Db=gene&Cmd=ShowDetailView&TermToSearch=8678

ATG5
http://www.ncbi.nlm.nih.gov/sites/entrez?Db=gene&Cmd=ShowDetailView&TermToSearch=9474

BCL2
http://www.ncbi.nlm.nih.gov/sites/entrez?Db=gene&Cmd=ShowDetailView&TermToSearch=596

AUTOPHAGY

Surviving the tumour suppressor

Autophagy — the breakdown of cellular proteins and organelles to sustain metabolism during starvation and metabolic stress — is thought to be a cell survival and, paradoxically, a cell death pathway. So why are genes that regulate autophagy selected against during tumorigenesis if loss of autophagy impairs tumour cell survival? Eileen White and colleagues might have found a mechanism that squares this circle.

Cells that are defective in autophagy (owing to allelic loss of beclin-1 (*BECN1*) or deficiency in another autophagy gene such as *ATG5*) are susceptible to metabolic stress. However, the allelic loss of *BECN1* increases tumorigenesis and this is augmented by apoptotic defects. To investigate this conundrum, White and colleagues produced several immortalized baby mouse kidney epithelial cell lines derived from either *Becn1* wild-type or heterozygous mice. They then engineered these cells to express the anti-apoptotic protein BCL2 or a control vector. They verified that $Becn1^{+/-}$;*Bcl2* cells had reduced survival under conditions of metabolic stress and were less able to recover from this stress, but were more tumorigenic. The authors reasoned that the impairment of autophagy might increase DNA damage, and they found that $Becn1^{+/-}$;*Bcl2* cells showed high levels of γH2AX foci formation, a marker of a DNA damage response. Further investigation showed that $Becn1^{+/-}$;*Bcl2* cells have centrosome abnormalities, are aneuploid, have numerical and structural chromosomal alterations and are prone to gene amplification. The authors verified these findings in *Atg5* wild-type, heterozygous and homozygous cells. So, in situations where cells are unable to undergo apoptosis, the induction of autophagy can promote survival and suppress genomic instability as a tumour-suppressive mechanism. Although the loss of autophagy initially impairs the survival of cells with defective apoptotic pathways, it seems likely that the onset of genomic instability offsets this negative over time.

The authors raise the possibility that drugs that induce autophagy might be useful cancer chemopreventive agents that limit cellular damage leading to chromosomal instability. Alternatively, inhibiting autophagy-mediated survival in more advanced tumours might sensitize tumour cells to metabolic stress and facilitate tumour regression. However, the status of the p53 and retinoblastoma tumour-suppressor pathways would need to be established, as the loss of these pathways (shown by the use of immortalized cells in this series of experiments) seems likely to increase the genomic instability of tumour cells.

Nicola McCarthy, Senior Editor,
Nature Reviews Cancer

ORIGINAL RESEARCH PAPER Mathew, R. *et al.* Autophagy suppresses tumour progression by limiting chromosomal instability. *Genes Dev.* **21**, 1367–1381 (2007)
FURTHER READING Lum, J. J. *et al.* Autophagy in metazoans: cell survival in the land of plenty. *Nature Rev. Mol. Cell Biol.* **6**, 439–448 (2005) | Baehrecke, E. H. Autophagy: dual roles in life and death? *Nature Rev. Mol. Cell Biol.* **6**, 505–510 (2005)