10-YEAR ANNIVERSARY

The importance of 'self-eating'

During autophagy, double-membrane structures called autophagosomes engulf cytosol or organelles and deliver them to lysosomes to be degraded and released as nutrients. Few scientists need this explanation now, but this wasn't true a decade ago when the molecular control of mammalian autophagy was only beginning to emerge. The finding that autophagy is implicated in human pathophysiologies, including tumorigenesis and neurodegeneration, highlighted its crucial role as a dynamic and selective cellular process.

In 2003, beclin 1 (*BECN1*; also known as autophagy-related gene 6 (*ATG6*)), the protein product of which is required for autophagosome formation, was established as a haploinsufficient tumour suppressor gene. Driven to understand why *BECN1* was monoallelically deleted in up to 75% of human sporadic breast, ovarian and prostate cancers, Qu *et al.* generated *Becn1*$^{+/-}$ mice, which showed an increase in the frequency of spontaneous malignancies and cell proliferation, and reduced autophagy, *in vivo*. Yue *et al.* found that *Becn1*$^{-/-}$ mice died early in embryogenesis and that *Becn1*$^{+/-}$ mice had a high incidence of tumours. Furthermore, *Becn1*$^{-/-}$ mouse embryonic stem cells were deficient in their autophagic response. These studies established that BECN1 and consequently autophagy have a role in tumour suppression.

Autophagy was linked to neurodegeneration in 2002 when Ravikumar *et al.* found that aggregate-prone proteins that are typically associated with Alzheimer's disease accumulated in cells treated with autophagy inhibitors, whereas the stimulation of autophagy enhanced their clearance, suggesting that autophagy protects against neurodegeneration. Komatsu *et al.* provided further evidence for this in 2006 when they found that mice lacking the essential autophagy gene *Atg7* in the nervous system showed behavioural defects and neuronal loss. At the same time, Hara *et al.* showed that mice deficient for *Atg5* in neural cells develop defects in motor function and accumulate cytoplasmic inclusion bodies in neurons. Thus, these studies showed that basal autophagy has a role in preventing neurodegeneration, highlighting the possibility that it might be protective in other diseases. Indeed, "all of us are relying on autophagy to protect us from various diseases, even if we are healthy", says Daniel Klionsky at the University of Michigan, USA.

Now that autophagy is firmly linked to human pathophysiology, the emphasis is on understanding its selectivity in particular conditions and the subcellular membrane trafficking events that contribute to this. The hope is that the next decade could see the development of disease therapies that target the autophagic pathway.

Katharine H. Wrighton

ORIGINAL RESEARCH PAPERS Qu, X. *et al.* Promotion of tumorigenesis by heterozygous disruption of the beclin 1 autophagy gene. *J. Clin. Invest.* **112**, 1809–1820 (2003) | Yue, Z. *et al.* Beclin 1, an autophagy gene essential for early embryonic development, is a haploinsufficient tumor suppressor. *Proc. Natl Acad. Sci. USA* **100**, 15077–15082 (2003) | Ravikumar, B. Duden, R. & Rubinsztein D. C. Aggregate-prone proteins with polyglutamine and polyalanine expansions are degraded by autophagy. *Hum. Mol. Genet.* **11**, 1107–1117 (2002) | Komatsu, M. *et al.* Loss of autophagy in the central nervous system causes neurodegeneration in mice. *Nature* **441**, 880–884 (2006) | Hara, T. *et al.* Suppression of basal autophagy in neural cells causes neurodegenerative disease in mice. *Nature* **441**, 885–889 (2006)
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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> *Daniel Klionsky, University of Michigan, USA*