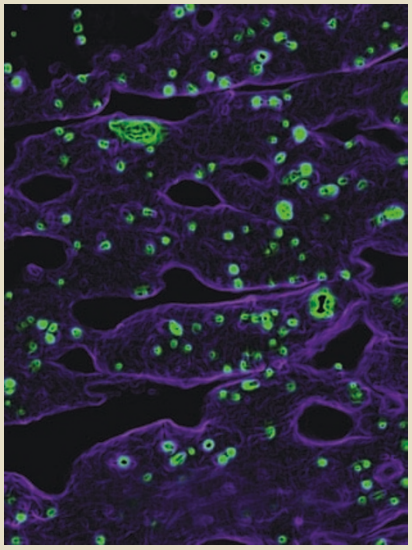
Autophagy: to die or not to die

When extracellular nutrients or growth factors are limited, eukaryotic cells sequester cytoplasmic components into phagosome vesicles to be targeted for lysosomal degradation, in a process known as autophagy. It is unclear, however, whether cells use 'self-digestion' as a means of survival by providing an alternative, intracellular energy source or whether autophagy is yet another cell death pathway, distinct from apoptosis or necrosis. Levine and colleagues report (*Cell* **122,** 927; 2005) that the anti-apoptotic protein Bcl-2 functions to limit autophagy to levels compatible with cell survival.

The authors showed that exogenous expression of cellular or viral Bcl-2 inhibits starvation-induced autophagy in both yeast and mammalian cells. In contrast, downregulation of Bcl-2 increases formation of autophagososmes under these conditions. By crossing mice transgenically expressing Bcl-2 with mice expressing a fluorescently labelled autophagy marker, the authors observed that after prolonged starvation, the levels of autophagy were decreased in cardiomyocytes of Bcl-2 expressing mice compared with control mice, thus establishing a physiological role for Bcl-2 in the regulation of this lysosomal pathway. Bcl-2 is an established regulator of apoptosis and even though additional functions have been attributed to Bcl-2 family members, its role in the lysosomal pathway may be another way that it controls cell homeostasis. Intriguingly, Bcl-2 seems to inhibit autophagy at the endoplasmic reticulum, rather than at mitochondria where it is known to regulate apoptosis. So how does Bcl-2 prevent autophagy at the ER?

Beclin-1 participates in the formation of autophagosomes and was identified as a Bcl-2-interacting partner. The authors found that Bcl-2 expression could rescue cells from Beclin-1–induced autophagy and that this required a physical interaction between the two proteins: Beclin-1 mutants defective in their ability to bind to Bcl-2, or Bcl-2 mutants defective in binding Beclin-1, blocked Bcl-2-mediated inhibition of autophagy. Furthermore, Beclin-1 mutants that cannot bind Bcl-2 induced autophagy-dependent cell-death and increased basal levels of autophagy even under conditions of normal growth. This could be blocked by short-interfering RNA (siRNA)-mediated downregulation of the downstream autophagy gene, *atg5*. Beclin-1's function in autophagy depends on its interaction with Class III PI(3)K but whether Bcl-2's inhibitory role is to disrupt the Beclin-1/Class III PI(3)K interaction remains unclear.



Bcl-2 transgenic expression reduces the number of autophagosomes (green dots) in cardiac muscle cells. A light microscopic image of starved mouse heart is shown, transgenically expressing the fluorescently tagged autophagy protein marker GFP-LC3. Image reproduced from Pattingre *et al. Cell* **122,** cover (2005), with permission from Elsevier (2005).

Collectively, this work demonstrates that the Bcl-2–Beclin-1 interaction acts as a threshold to keep the levels of autophagy in check. This is further supported by the finding that Beclin-1 and Bcl-2 associate in a nutrient-dependent manner, whereby starvation decreases the amount of Beclin-1 bound to Bcl-2 and nutrient availability has the opposite effect. Future experiments will hopefully uncover the mechanism that tips the fragile balance of cell survival and cell death.

MYRTO RAFTOPOULOU