APOPTOSIS

Fragments of death

The study of apoptosis is synonymous with the nematode *Caenorhabditis elegans*, as many of the important molecular components in this conserved biological process have been identified through genetic studies in this model organism. Now, reporting in *Nature*, Barbara Conradt and co-workers show that mitochondrial fragmentation — previously thought to be an exclusive characteristic of apoptotic mammalian cells — is also a feature of apoptosis in *C. elegans*. And by mutating the tractable genome of this useful organism, the researchers explain how mitochondrial break-up might contribute to the apoptotic process.

Although mitochondria had not previously been shown to have a crucial role in apoptosis in nematodes, it seemed unlikely that this organelle — such an enthusiastic participant in apoptosis in mammals — would be a mere 'innocent bystander' in the *C. elegans* cell-death programme. So Conradt and her team examined live *C. elegans* embryos using time-lapse confocal microscopy and noted the morphology of mitochondria in cells that were undergoing programmed cell death. They observed that, in non-apoptotic cells, mitochondria formed a cohesive network of tubules. However, soon after the induction of apoptosis, the network started to break up until only mitochondrial fragments remained in the cell.

But is the fragmentation of mitochondria a causal event in apoptosis, or simply a morphological phenomenon in a dying cell? Conradt and co-workers tackled this question by expressing a dominant-negative mutant of the mitochondrial-fission-promoting protein DRP-1 in *C. elegans* embryos, thereby inhibiting mitochondrial break-up. This inhibition of mitochondrial fragmentation prevented apoptosis in ~20% of cells in these transgenic animals. Importantly, the overexpression of wild-type *drp-1* during embryogenesis increased mitochondrial disintegration and also increased the number of cells that died by apoptosis.

Using loss-of-function and gain-of-function mutant embryos, the

DEVELOPMENT

Youth is overrated

It has long been thought that regenerating cells undergo a rejuvenation process to achieve pluripotency. However, a new study in *Cell* by Sustar and Schubiger challenges this view by showing that regenerating cells in *Drosophila melanogaster* imaginal discs do not revert to a 'younger', faster cell cycle — but instead have a unique cell cycle profile with characteristics of both younger and older cells.

Imaginal discs are small groups of epithelial cells that become determined late in larval development to form specific structures, such as wings and legs. The process of transdetermination in *D. melanogaster* imaginal discs is a well-characterized model system for cell plasticity. Transdetermination can be induced by disc injury ('disc fragmentation') or activation of the Wnt-family *wingless* (*wg*) gene, which causes a change in cell fate — for example, from leg to wing — of a small subset of regenerating cells in a region of the disc known as the 'weak point'.

To find out whether regenerating cells in fragmented imaginal discs rejuvenate, Sustar and Schubiger analysed their cell cycle profile and doubling time. The cells did not revert to a 'younger' cell cycle with a shorter doubling time, and maintained a profile that was similar to that of unfragmented disc cells of the same age.

Induction of the Wg signalling pathway activates the enhancer of the *vestigial* (*vg*) selector gene, which is necessary for wing development and the induction of leg-to-wing transdetermination. To visualize leg-to-wing transdetermination, the authors used the *vg* regulatory element to make a fluorescent reporter construct. Following Wg overexpression, disc cells initially divided asynchronously, but after ~2 days, cells in S phase were exclusively localized in the weak point region. This change in the cell cycle occurred before the reporter gene was visibly expressed and, therefore, before transdetermination. In the early phase of transdetermination, a greater proportion of transdetermining cells were in S phase compared with non-transdetermining cells and later, the cell cycle profile reverted to that of non-transdetermining cells. Strikingly, the cell cycle profile in the early phase of transdetermination was unique and did not match that of any specific developmental stage.

So, Wg induction seems to trigger an alteration in the cell cycle of transdetermining cells in the weak point. In addition, these cells are initially considerably larger than non-regenerating cells. So, might cell cycle induction or the activation of cell growth be sufficient to induce transdetermination? Sustar and Schubiger overexpressed several cell cycle and cell growth genes. They found that overexpression of the insulin receptor gene or *Ras*, but not other genes, mimicked the effects of Wg induction. The authors propose, however, that transdetermination probably requires more than a growth signal, and they suggest that Wg expression in the weak point has multiple functions — growth activation and an increase in developmental plasticity.

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References and links

ORIGINAL RESEARCH PAPER Sustar, A. & Schubiger, G. A transient cell cycle shift in *Drosophila* imaginal disc cells precedes multipotency. *Cell* **120**, 383–393 (2005)

FURTHER READING Johnston, L. A. Regeneration and transdetermination: new tricks from old cells. *Cell* **120**, 288–290 (2005)