DEVELOPMENT

Leading a programmed death

Non-apoptotic cell death is important during animal development, but the genes controlling this type of cell death are unknown. Blum *et al.* identify *pqn-41*, which encodes a poly-Glu-repeat protein, as a gene required for linker cell death in *Caenorhabditis elegans*.

During development of the male reproductive system of *C. elegans*, the linker cell leads the migration and elongation of the male gonad and then dies between the fourth larval stage and adulthood. Linker cell death is controlled by a cell-autonomous process that does not involve any of the known cell death factors — such as apoptotic caspases — and is characterized by specific morphological features; these include indentation of the nuclear envelope, uncondensed chromatin and organelle swelling.

In an RNA interference-based screen for genes required for linker cell death, the authors identified *pqn-41* as the only gene, among six clones, exclusively affecting linker cell survival. Surviving linker cells lacking *pqn-41* expression did not show any nuclear envelope indentations but did show organelle swelling, indicating that PQN-41 is required for the former but not the latter. Furthermore, inactivation of *pqn-41* specifically in linker cells was sufficient for survival, which suggests that PQN-41 functions cell-autonomously.

pqn-41 encodes a protein containing Glu-rich domains that form six coiled-coil motifs. Protein truncations showed that these coiled-coil regions are necessary for PQN-41 function in promoting cell death. These motifs can be found in prions and in aggregation-prone proteins, which are associated with neurodegenerative diseases. PQN-41 fused to green fluorescent protein formed cytoplasmic aggregates in the linker cell, suggesting that PQN-41 shares structural similarities with those proteins. Importantly, although poly-Glu repeats are often toxic for cells, expression of PQN-41 in cells other than linker cells did not induce death, which indicates that PQN-41 requires the appropriate cellular context to promote death.

> “PQN-41-like proteins might mediate non-apoptotic developmental cell death in vertebrates”

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Blum *et al.* went on to analyse *pqn-41* expression and found that it is turned on in linker cells when they begin to die. Furthermore, they identified the mitogen-activated protein kinase kinase SEK-1 as an upstream regulator that is required for *pqn-41* expression. Interestingly, the authors observed that the zinc-finger transcription factor LIN-29, which had previously been shown to be involved in linker cell death, does not affect *pqn-41* expression. This suggests that SEK-1 and LIN-29 function in parallel, and this was confirmed by the additive effect seen in worms carrying loss-of-function mutations in both genes.

Linker cell death shares morphological similarities with vertebrate developmental cell death, raising the possibility that PQN-41-like proteins might mediate non-apoptotic developmental cell death in vertebrates. In addition, nuclear envelope indentation is seen in poly-Glu expansions underlying neurodegenerative diseases, so it is possible that these proteins might promote neurodegeneration by inappropriately activating a type of cell death similar to that of linker cells.

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ORIGINAL RESEARCH PAPER Blum, E. S. *et al.* Control of nonapoptotic developmental cell death in *Caenorhabditis elegans* by a polyglutamine-repeat protein. *Science* **335**, 970–973 (2012)