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AXON DEGENERATION

A new pathway emerges

Degeneration of an axon distal to the injury site — termed Wallerian degeneration — is thought to involve an active process that is similar to apoptosis, but direct evidence for the existence of such an axon death pathway has remained elusive. Now, Freeman and colleagues show that the loss of function of the gene *dSarm* (also known as *Ect4*) in *Drosophila melanogaster* or its orthologue *Sarm1* in mice protects against injury-induced axon death, suggesting that Wallerian degeneration is indeed driven by a dedicated, and conserved, axonal death programme.

The authors first conducted extensive screens of fly mutations that are known to affect apoptosis, autophagy or other well-characterized cell death pathways to see whether they could also inhibit Wallerian degeneration. None of these mutations seemed to suppress this process, so the authors performed a forward genetics screen from which they identified three mutant lines of flies that demonstrated axonal preservation for weeks after axotomy. These levels of preservation rivalled those seen in *D. melanogaster* harbouring the Wld^S mutation — a gain of function mutation that protects against Wallerian degeneration. Importantly, apoptotic processes were preserved in all three mutant lines.

Next, using small chromosome deficiencies and next-generation sequencing technology, the authors identified the gene underlying the phenotypes of these three mutated flies as *dSarm*. Expression of a full-length *dSarm* cDNA in these mutants ablated the suppression of axonal degeneration, confirming that the phenotypes of axonal preservation in these flies result from the loss of function of *dSarm*.

The authors then examined $Sarm1^{-/-}$ mice and found that cultures of superior cervical ganglia, cortical neural axons and dorsal root ganglia from these animals all exhibited robust protection from degeneration up to 72 hours after axotomy, similar to neuronal cultures from Wld^S mice. Moreover, *in vivo*, lesioned axons in $Sarm1^{-/-}$ mice were protected from destruction for at least 14 days after injury, which was attributed to a concomitant suppression of macrophage and monocyte infiltration.

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Together, these data show that *dSarm/Sarm1* is a component of a specific axonal death programme that is triggered following axotomy and seems to be conserved from flies to mammals.

Man Tsuey Tse

ORIGINAL RESEARCH PAPER Osterloh, J. M. *et al.* dSarm/Sarm1 is required for activation of an injury-induced axon death pathway. *Science* 7 Jun 2012 (doi:10.1126/science.1223899)