AXON DEGENERATION

Committing to a break up

The stereotypical pattern of events known as Wallerian degeneration that occurs in axons in response to various physical and chemical insults is thought to be driven by a common signalling pathway; however, the molecular components of this pathway are unknown. A new paper by DiAntonio and colleagues now unveils dual leucine kinase (DLK; also known as MAP3K12) as an important component of the axonal self-destruct programme.

To determine whether DLK has a role in axonal self-destruction the authors removed the antennae of *Drosophila melanogaster*, axotomizing the olfactory receptor neurons (ORNs) that project from these sensory structures to the brain. Unlike the ORN axons of their wild-type counterparts, which degenerated within 24 h, the severed axons of flies lacking *wnd* — the fly orthologue of *DLK* — exhibited significant preservation. Restoring *wnd* expression in the mutant ORNs abolished this protection, indicating that the protein acts in axons to promote their degeneration.

Extending these findings to mammals, the authors showed that cultured dorsal root ganglion (DRG) neurons from mice lacking DLK were resistant to degeneration following axotomy or treatment with the chemotherapeutic drug vincristine. Furthermore, mice lacking DLK demonstrated axonal preservation following sciatic nerve injury *in vivo*, confirming the importance of DLK in mammalian axon degeneration.

To identify the mediators of DLK's effects, the authors treated DRG cultures with pharmacological inhibitors of its downstream effectors, Jun N-terminal kinase (JNK; also known as MAPK8) and p38 (also known as MAPK14). Inhibiting JNK protected axons against axotomy-induced degeneration, whereas p38 inhibitors had no effect. However, inhibiting JNK either immediately prior to or 3 h after axotomy was ineffective, indicating that this kinase contributes to the 'commitment to degenerate' phase of Wallerian degeneration that takes place after injury but before axonal fragmentation ensues.

These results support the concept of a common pathway by which multiple insults trigger Wallerian axon degeneration and shed light on two of the key components of this pathway, a finding that may have significance for the development of therapeutics to combat axon degeneration.

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ORIGINAL RESEARCH PAPER Miller, B. R. *et al.* A dual leucine kinase–dependent axon self-destruction program promotes Wallerian degeneration. *Nature Neurosci.* **12**, 387–389 (2009)