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„Molecular regulation of axon degeneration”

Traditionally, it has been believed that axons are highly dependent on their cell bodies for long-term survival. However, recent studies point to the existence of axon-autonomous mechanism(s) that regulate rapid axon degeneration after axotomy. Here, we review the cellular and molecular events that underlie this process, termed Wallerian degeneration. The slow Wallerian degeneration gene, *Wld*^{S}, delays Wallerian degeneration and axon pathology for several weeks in mice and rats. Interestingly, neuronal cell death is also delayed in some *in vivo* models, most strikingly in the progressive motoneuronopathy mouse. We describe the biphasic nature of axon degeneration after axotomy and our current understanding of how *Wld*^{S}--an extraordinary protein formed by fusing a Ube4b sequence to Nmnat1-- acts to protect severed axons. Interestingly, the neuroprotective effects of *Wld*^{S} span all species tested, which suggests that there is an ancient, *Wld*^{S}-sensitive axon destruction program. Wld^S does not directly prevent death of motoneuron cell bodies. It follows that the protection of neuronal cell bodies observed in several disease and injury models where axons or significant axonal stumps remain is most probably secondary to axonal protection.

The NAD(+) synthesizing enzyme NMNAT1 constitutes most of the sequence of

neuroprotective protein Wld(S), which delays axon degeneration by 10-fold. NMNAT1 activity is necessary but not sufficient for Wld(S) neuroprotection in mice and 70 amino acids at the N-terminus of Wld(S), derived from polyubiquitination factor Ube4b, enhance axon protection by NMNAT1. NMNAT1 activity can confer neuroprotection when redistributed outside the nucleus or when highly overexpressed in vitro and partially in Drosophila. However, the role of endogenous NMNAT1 in normal axon maintenance and in Wallerian degeneration has not been elucidated yet. Heterozygous Nmnat1 knockout mice develop normally and do not show spontaneous neurodegeneration or axon pathology. Wallerian degeneration after sciatic nerve lesion is neither accelerated nor delayed in these mice, consistent with the proposal that other endogenous NMNAT isoforms play a principal role in Wallerian degeneration.

Axonal degeneration has been proposed to be mediated by an active autodestruction program, akin to apoptotic cell death; however, loss of function mutations capable of potently blocking axon self-destruction have not been described. We show that loss of the Drosophila Toll receptor adaptor dSarm (sterile α/Armadillo/Toll-Interleukin receptor homology domain protein) cell-autonomously suppresses Wallerian degeneration for weeks after axotomy. Severed mouse Sarm1 null axons exhibit remarkable long-term survival both in vivo and in vitro, indicating that Sarm1 prodegenerative signaling is conserved in mammals. Our results provide direct evidence that axons actively promote their own destruction after injury and identify dSarm/Sarm1 as a member of an ancient axon death signaling pathway.