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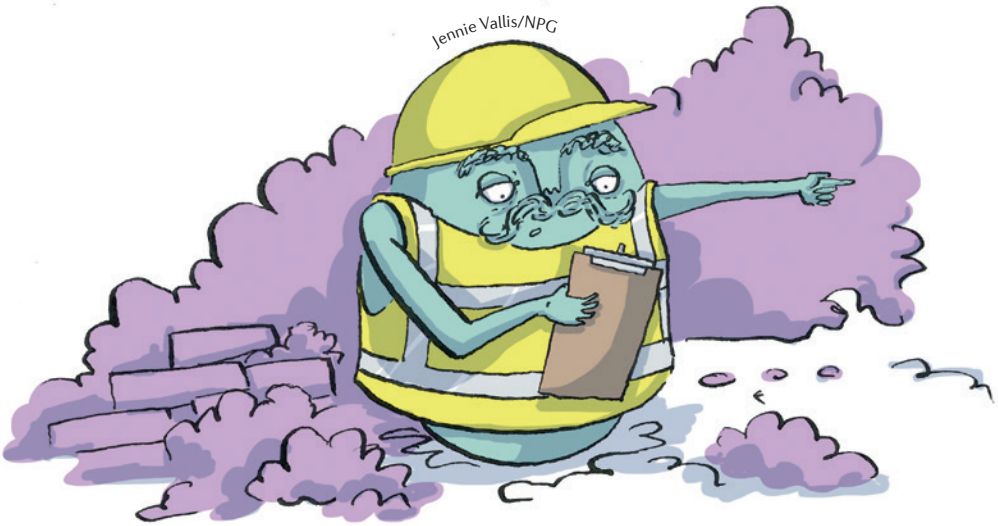

NEURAL REPAIR

Redirecting regeneration

Injured axons in the peripheral nervous system (PNS) can regenerate and reform connections with their original target; however, the molecular basis for this pathfinding is not clear. In a new study, Granato and colleagues show that extracellular matrix (ECM) components help to direct regenerating motor axons in zebrafish to their original targets.

In zebrafish, each motor nerve that projects from the spinal cord branches into two bundles of axons: one innervating the dorsal myotome and one projecting to the ventral myotome. After laser transection of the motor nerve proximal to the point at which the dorsal and ventral nerve branches separate, the injured axons regenerated and reinnervated their original respective targets within ~48 hours. Live-cell imaging revealed that, 7–11 hours after similar transection of only the dorsal nerve branch, axonal growth cones of the regenerating neurons showed repeated extension and retraction. This finding led the authors to hypothesize that, rather than just following an intrinsic programme, these growth cones may be guided by extrinsic cues, possibly in the ECM.

The enzyme lysyl hydroxylase 3 (Lh3) prepares certain ECM collagens for secretion and is important during motor nerve development. To test whether Lh3 is also important during nerve regeneration, the authors created zebrafish in which Lh3 expression was induced during development but, unlike in wild-type zebrafish, was no longer detectable by 4 days post-fertilization (Lh3 mutants). The regenerating neurons of Lh3 mutants in which the dorsal nerve branch had been transected at 5 days post-fertilization were less likely than those of wild-type controls to follow their original trajectory; many Lh3-mutant axons showed ectopic projection into ventral or ventrolateral territories. Thus, Lh3 is required for target-specific regrowth of dorsal nerve axons.

Collagen type IV α5 (Col4α5) is one of the ECM protein substrates of Lh3, and binds to Slit1a, an ECM protein that is involved in axon repulsion. Double *in situ* hybridization revealed that the mRNA expression of both *col4a5* and *slit1a* was upregulated in Schwann cells immediately ventral or lateral to the dorsal nerve transection. Furthermore, zebrafish lacking functional Col4α5 showed aberrant regrowth of transected dorsal nerves that was similar to that seen in the Lh3 mutants. Restoring Lh3 expression — and thus Col4α5 processing — specifically in the Schwann cells of Lh3 mutants enabled the on-target regeneration of dorsal nerve branches, confirming that Schwann-cell-derived Col4α5 is key to this process.

This study provides evidence that certain Schwann-cell-secreted ECM molecules can act as cues for the direction-specific regeneration of PNS neurons. The authors suggest that, after motor nerve injury, Col4α5 and Slit1a secreted by Schwann cells in ventral or ventrolateral territories may accumulate to form a repellant barrier that prevents the stabilization of regenerating dorsal nerve axons along the 'wrong' trajectory.

> "many Lh3-mutant axons showed ectopic projection into ventral or ventrolateral territories"

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ORIGINAL ARTICLE Isaacman-Beck, J. *et al.* The *lh3* glycosyltransferase directs target-selective peripheral nerve regeneration. *Neuron* http://dx.doi.org/10.1016/j.neuron.2015.10.004 (2015)