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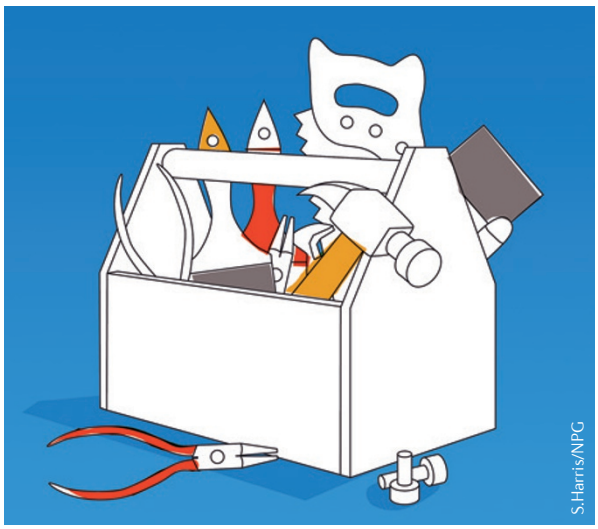
CNS INJURY

Microtubule stabilizer repairs spinal cord injury

Spinal cord injury (SCI) often results in permanent neurological impairment owing to the formation of scar tissue, which inhibits axon regeneration. Now, writing in *Science*, Ruschel *et al.* show that microtubule stabilization using the anticancer agent epothilone B (epoB) decreases scarring and stimulates axon regrowth, resulting in restoration of locomotive function in a rat SCI model.

Previous work showed that microtubule stabilization using the US Food and Drug Administration (FDA)-approved anticancer drug paclitaxel reduces scarring and promotes axon growth in rodent SCI models. However, the cellular mechanisms mediating these effects remain unclear. Moreover, paclitaxel cannot be used clinically, as it is unable to cross the blood–brain barrier (BBB).



With this in mind, Ruschel *et al.* set out to further understand the cellular effects of microtubule stabilization and to target this process in a clinically feasible way.

The authors focused their studies on epoB, a BBB-permeable microtubule-stabilizing drug that is also approved for cancer treatment. Rats that were systemically administered with epoB at day 1 and day 15 after dorsal spinal cord hemisection (DSCH) showed increased microtubule stability in lesion site extracts, and reduced scar tissue formation at 4 weeks, compared to vehicle-treated rats, without any adverse effects.

Next, the authors investigated the cellular effects of epoB. In *in vitro* wound-healing assays, epoB changed the microtubular network of scar-forming rat meningeal fibroblasts: it elevated levels of stable detyrosinated microtubules, which prevented fibroblast polarization and migration to the injury site. Likewise, systemic administration of epoB to rats at day 1 and day 15 after DSCH prevented the polarization of meningeal fibroblasts into a bipolar shape, thus inhibiting their migration to the lesion site.

In co-cultures of rat meningeal fibroblasts and postnatal cortical neurons, epoB treatment similarly disrupted fibroblast polarization. In cortical neurons, epoB induced rapid polymerization of microtubules into the neurite tips, causing axon elongation; these effects were abolished by the microtubule-destabilizing drug nocodazole.

The authors then assessed the ability of epoB to promote axon regeneration *in vivo*. In adult mice injected with epoB following DSCH, transected axons exhibited significantly fewer retraction bulbs (formed by injured axons), reduced axonal dieback and increased regenerative growth. Moreover, systemic epoB treatment promoted axon regeneration after complete dorsal column transection.

Finally, Ruschel and colleagues assessed the effects of epoB on locomotive function. Adult rats systemically treated with epoB at day 1 and day 15 post DSCH exhibited a threefold increase in serotonergic fibres — which have been implicated in the recovery of motor function — caudal to the injury. Furthermore, in rats that underwent moderate, mid-thoracic spinal cord contusion — a clinically relevant SCI model — systemic epoB treatment reduced fibrotic scarring at the injury site, promoted serotonergic axon regrowth in the caudal spinal cord, increased stride length and gait regularity, and improved walking balance and coordination.

Together, these findings provide promise for functional recovery after SCI and highlight epothilones as a potential treatment approach.

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ORIGINAL RESEARCH PAPER Ruschel, J. *et al.* Systemic administration of epothilone B promotes axon regeneration after spinal cord injury. *Science* http://dx.doi.org/doi:10.1126/science.aaa2958 (2015)