to speculate that such a broadly represented population contains further subsets of specialized fibroblasts. Furthermore, it is not entirely clear how this large population originates from a very small pool of precursors in skin at early embryonic time points, nor where other fibroblast-type, mesenchymal cell subsets fit into their lineage partition, such as hair follicle–associated dermal papilla and sheath cells and vascular smooth muscle cells. In addition, the results of this study focus primarily on the fibrogenic activity of En1-lineage–positive cells, leaving us to wonder about the origins and purpose of the lineage-negative cells that constitute at least 30% of adult skin fibroblasts.

Finally, the authors used a cell surface marker screen to identify *CD26/Dpp4* as a unique label for En1 fate-mapped fibrogenic fibroblasts in adult skin. Subsequent experiments revealed that prospectively isolated adult $CD26^+$ mesenchymal cells primarily contributed ECM components during wound-healing and tumor response assays. More intriguingly, the authors observed a slight but significant difference in fibrogenic gene expression between $CD26^+$ and $CD26^-$ fibroblasts that was greatly exacerbated by a wounding assay stimulus. Thus, although fibroblasts from separate lineages are intrinsically similar at baseline, they are unique in their individual transcriptional and functional responses to signals from within the greater milieu of the skin.

Not only is *CD26/Dpp4* useful for isolating or identifying fibrogenic cells in situ, but the discovery is also clinically relevant. *Dpp4* signaling itself appears to coordinate fibrogenic activity, and the authors could mitigate scar size during healing by applying a specific *Dpp4* inhibitor to wound sites. This discovery has far-reaching implications for drug development, provided the observation proves relevant to wound healing in human skin as well. Furthermore, the utility of *Dpp4* as a marker or druggable target might also be applicable to studying or treating fibrosis in organs outside of the skin. ■

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NEUROSCIENCE

Systemically treating spinal cord injury

A drug that crosses the blood-brain barrier has therapeutic potential for central nervous system trauma

By **Amanda P. Tran** *and* **Jerry Silver**

Spinal cord injury is a debilitating condition. Axons of nerve cells are severed, resulting in a range of deficits, including the loss of voluntary movements and sensation. Failure of axonal regeneration after such an injury may be partly explained by a decreased intrinsic capacity for neuron growth, especially at the lesion site (*1*). On page 347 in this issue, Ruschel *et al.* (*2*) show that this inhibition can be overcome with a small molecule that can be injected into the body cavity, cross the blood-brain barrier, and reach the central nervous system. The drug, epothilone B, stabilizes microtubules in extending axons, thereby promoting spinal cord regeneration.

Upon approaching the glial scar at the lesion site of the spinal cord, the tips of regenerating axons form swollen dystrophic growth cones (*3*). These were first described as "sterile clubs" by the neuroscientist and Nobel laureate Ramón y Cajal, who also believed that they persisted only briefly in a quiescent state before the axon "died back" to a sustaining collateral (now defined as a branch off the main axon that feeds back onto the neuron's cell body) (*4*). By contrast, Ruschel *et al.* describe how dystrophic growth cones remain in the injured human spinal cord for a remarkable 42 years after injury. Advances in in vivo imaging have also revealed that, for a time, dystrophic growth cones are dynamic and can regenerate in a more accommodating environment (*5*). Moreover, dystrophic growth cones eventually form synaptic-like relationships with oligodendrocyte precursor cells in the lesion core, enabling them to persist for long periods (*6*, *7*).

Electron micrographs of adult rats with spinal cord injury illustrated that dystrophic growth cones are bloated with disorganized microtubules arranged in nonparallel networks (*8*). To better understand the internal machinery of dystrophic growth cones and determine whether they are malleable, earlier studies assessed the effects of the anticancer drug paclitaxel (Taxol). Paclitaxel belongs to the taxane family of drugs that targets tubulin. It stabilizes microtubule polymers and protects them from disassembly. Suppression of microtubule dynamics thus interferes with cellular processes such as cell division and cell motility. Indeed, it was shown that caged Taxol (which could be activated in a restricted area) specifically stabilized the dystrophic growth cone microtubule cytoskeleton in cultured rat neurons, and that this was sufficient for axon formation (*9*). This effect was reversed with nocodazole, a microtubule-destabilizing drug (*8*, *9*). Intrathecal delivery (injection into the spinal fluid) of Taxol following a dorsal hemisection of the rat spinal cord also promoted microtubule stabilization, allowing increased axonal penetration through the glial scar (*10*). Taxol additionally decreased the ability of transforming growth factor–β1 to adversely affect rearrangement of the cytoskeleton in astrocytes, which reduced scarring induced by spinal cord injury (*10*).

> ***"...there are currently no drugs approved...to treat this traumatic injury that allow for functional recovery."***

Using a more clinically relevant microtubule stabilization strategy as a putative spinal cord injury therapy, Ruschel *et al.* tested epothilone B in different rat models of spinal cord injury. Epothilone B also targets tubulin, but is a member of a different family of drugs. Unlike Taxol, it penetrates the blood-brain barrier, as seen through mass spectrometry analysis of rat spinal cord tissue after intraperitoneal delivery (injection into the body cavity). Ruschel *et al.* found that by stabilizing microtubules, epothilone B enhanced axon regeneration and ultimately improved sensorimotor function in an injured rat, boosting intrinsic axonal growth while reducing axon-inhibitory scarring after injury.

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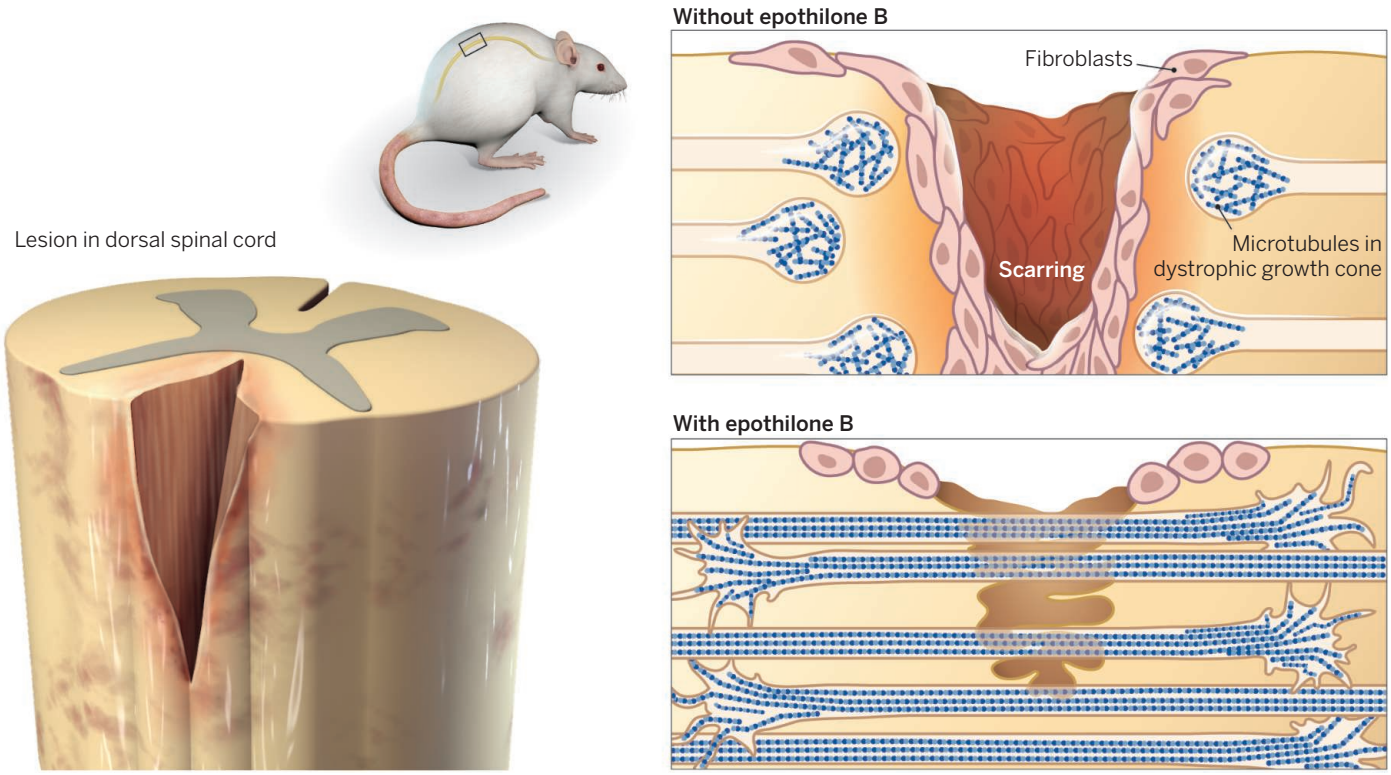

Dual acting drug. After spinal cord injury, dystrophic growth cones fill with disorganized microtubules and axons cannot extend. Fibroblasts migrate to the lesion and contribute to an environment that inhibits axon outgrowth. Systematically delivered epothilone B, which crosses the blood-brain barrier, stabilizes neuron microtubules and promotes axon extension through the injured site. It also hampers fibroblast migration and scar formation.

Fibroblasts proliferate after spinal cord injury and contribute to scarring (*11*). Ruschel *et al.* observed that epothilone B attenuated fibrotic scar formation in vivo and propose that the effect may be due to the drug's ability to decrease fibroblast migration. Fibroblasts surrounding the edge of the dorsal hemisection lesion displayed a rounder shape and an increase in stabilized tubulin when exposed to the drug. Why is the drug's effect on fibroblasts seemingly opposite from its effect on neurons? The authors propose the difference may be due to epothilone B's interactions with tau, a microtubule-associating protein enriched in neurons.

Even more impressive is the ability of epothilone B to drive axon outgrowth (in vitro) across classically inhibitory substrates such as Nogo-A, chondroitin sulfate proteoglycans, and semaphorin 3A (an effect that was abolished with nocodazole). Injection of epothilone B into the rat body cavity after dorsal column transection transformed dystrophic growth cones into regenerating axons that could more readily penetrate the scar compared to injured animals injected with a control. After spinal contusion injury, epothilone B treatment increased sprouting of neurons containing the neurotransmitter serotonin. Interestingly, the addition of a serotonin antagonist abrogated gains in sensorimotor function, further substantiating the importance of this neuronal subtype in functional recovery after spinal cord injury (*12*). How serotonergic neurons respond to different treatments, including microtubule stabilization, and how they robustly sprout after injury remain pressing questions.

The value of epothilone B treatment after spinal cord injury lies in its ability to modulate both the inhibitory scar environment and the regenerating potential of neurons in a noninvasive manner (see the figure). The dual effects point to the potential of combinatorial strategies to target more than one underlying problem of a given condition, such as spinal cord injury. Moreover, systemically delivered drugs represent the next frontier of research in therapies for injuries of the central nervous system.

Aside from drugs that manage symptoms caused by spinal cord injury, there are currently no drugs approved by the U.S. Food and Drug Administration to treat this traumatic injury that allow for functional recovery. The systemic delivery of a drug such as epothilone B could therefore be a turning point in treatment. Additionally, one could combine this drug with intravenous delivery of synthetic platelets to stanch bleeding (*13*), and with an immune-modulating therapy to allow for neuroprotection, as bone marrow–derived activated macrophages have been shown to cross the blood-brain barrier and inhibit axon regeneration (*14*). This systemic "cocktail" could further include a drug that enables neuronal growth cones to bypass inhibitory components of the extracellular matrix (*15*). In this way, the differing molecular challenges of recovering from spinal cord injury may be overcome, without the risk of exposing the spinal cord, to allow for meaningful regeneration and ultimately functional recovery from a devastating condition. ■

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