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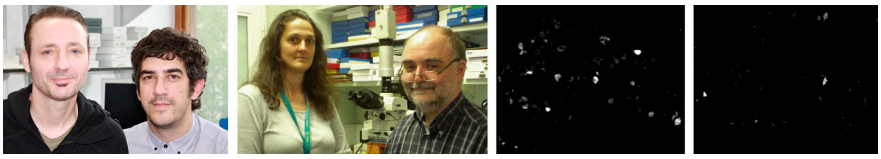
Schwann cells aid regeneration project

Study reveals how the expression of c-Jun in Schwann cells helps restore damaged nerves.

Focal Point



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(Left to right) Axel Behrens, Xavier Fontana, Mariya Hristova, Gennadij Raivich, and colleagues (not pictured) investigate how Schwann cells promote nerve regeneration by up-regulating the transcription factor c-Jun. In mice with c-Jun–deficient Schwann cells (far right), fewer facial neurons reconnect to the whisker pads after injury, as indicated by the decreased labeling of neuronal cell bodies compared with wild-type animals (second from right). c-Jun induces the expression of several signaling factors, including GDNF and Artemin, that signal to injured nerve cells to promote neuron survival and axonal outgrowth.

Unlike neurons in the central nervous system, peripheral nerves can regenerate after injury and reconnect to their target cells. Fontana et al. reveal how Schwann cells, which normally wrap an insulating myelin sheath around the axons of healthy peripheral neurons, boost the survival and regrowth of injured nerves by up-regulating the transcription factor c-Jun (1).

Axel Behrens, from the London Research Institute of Cancer Research UK, is interested in why different types of nerves have different regenerative capacities. "What is the difference between nerves that can regenerate and those that can't?" Behrens asks. "What are the factors required to make a neuron regrow?"

One event initiated by peripheral nerve injury is the dedifferentiation of the Schwann cells surrounding the damaged neuron into proliferative precursor cells that reactivate expression of c-Jun, a transcription factor that suppresses myelin production (2, 3). The de-differentiated Schwann cells promote axonal regrowth by altering the neuron's microenvironment (4, 5), but, says Behrens, "the significance of c-Jun up-regulation isn't known."

Collaborating with Gennadij Raivich's laboratory at University College London, Behrens and colleagues, led by Xavier Fontana and Mariya Hristova, therefore investigated neuronal regeneration in mice whose Schwann cells lacked c-Jun. In wild-type mice, the nerves that innervate facial muscles completely recover within a few weeks of being cut, restoring movement to the animals' whiskers. But regeneration was abolished in mice with c-Jun–deficient Schwann cells. "We found defects in both neuron survival and in the ability of the damaged axons to regrow toward the muscle," explains Fontana. As a result, the mutant mice failed to recover their whisker movements.

> **"What are the factors required to make a neuron regrow?"**

To understand how Schwann cell c-Jun promotes neuron regeneration, Fontana et al. searched for genes that were up-regulated in wild-type, but not mutant, Schwann cells after nerve injury. The researchers identified several neurotrophic factors that weren't induced in the absence of c-Jun, but they focused on two—GDNF and Artemin—that contained c-Jun binding sites in their promoter regions and that were therefore likely to be direct targets of the transcription factor (a hypothesis confirmed by experiments in cultured Schwann cells).

GDNF and Artemin are both ligands for the receptor tyrosine kinase Ret, which is expressed in neurons but not in Schwann cells. Fontana et al. found that activation of the Ret receptor was impaired in the injured neurons of mice whose Schwann cells lacked c-Jun, suggesting that Schwann cells usually secrete these neurotrophic molecules to aid neuronal recovery. Indeed, supplying exogenous GDNF and Artemin improved facial nerve regeneration in mice with c-Jun–deficient Schwann cells.

Mice whose neurons lacked the Ret receptor also showed decreased regenerative capacity. In these mice, severed facial nerves largely survived their injuries, but they failed to regrow their axons and reinnervate the animals' whiskers. "So we think that GDNF and Artemin signaling through Ret promotes axonal outgrowth," Behrens explains. "But the other neurotrophic factors up-regulated in Schwann cells by c-Jun, factors like LIF, NGF, and BDNF, probably contribute to neuronal survival."

"Our results show the complexity of axonal regeneration," Behrens continues. "Many cell types work together to achieve target reconnection."

Raivich, Behrens, and colleagues now want to investigate the functions of the other growth factors induced by c-Jun upon injury, but they also have larger questions about the pro-regenerative role of Schwann cells. "While some nerves have the ability to regenerate, some don't," notes Raivich. "Could a difference in Schwann cell function be the reason?"

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3. Parkinson, D.B., et al. 2008. *J. Cell Biol.* 181:625–637.
4. Parrinello, S., et al. 2010. *Cell.* 143:145–155.
5. Webber, C., and D. Zochodne. 2010. *Exp. Neurol.* 223:51–59.