Merlin weaves its magic on peripheral nerve repair

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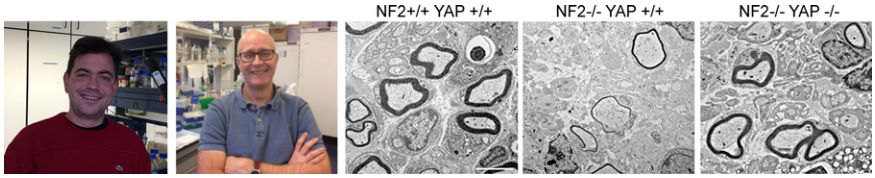
Tumor suppressor helps reprogram Schwann cells to promote peripheral nerve regeneration.



Focal Point Thomas Mindos (left), David Parkinson (right), and colleagues investigate the function of the tumor suppressor Merlin in Schwann cells. Development of the peripheral nervous system is largely unaffected by the removal of Schwann cell Merlin, but regeneration after injury is almost completely blocked because the Merlin-deficient Schwann cells fail to convert themselves into repair-competent Büngner cells capable of secreting neurotrophic growth factors. This is a result of elevated expression of the Hippo pathway effector, and transcriptional coactivator, YAP. 21 days after a crush injury, myelinated axons are abundant in the sciatic nerve of a wild-type mouse (left) but are largely absent in Merlin-deficient animals (middle). Axon regeneration and remyelination are restored in mice lacking both Merlin and YAP (right). Photos courtesy of the authors.

The peripheral nervous system (PNS) can regenerate after injury but this requires both the neurons and the Schwann cells that myelinate them to dramatically alter their behavior and activate a specialized program of repair. Schwann cells, for example, lose their myelin and become repair-competent "Büngner cells" that secrete neurotrophic growth factors as well as cytokines that recruit macrophages to the site of injury (1). Mindos et al. reveal that the tumor suppressor Merlin and its effector protein YAP control this switch in Schwann cell function to regulate PNS repair (2).

Merlin regulates several different signaling pathways that control cell proliferation and its loss leads to the formation of various nervous system tumors, including schwannomas, which arise from Schwann cells (3). To investigate Merlin's role in the normal development and function of the PNS, David Parkinson and colleagues at the University of Plymouth used conditional knockout mice that specifically lacked the protein in their Schwann cells. "We wanted to know what Merlin does during myelination, and the answer to that was very little!" explains Parkinson. Peripheral nerves developed relatively normally in the absence of Schwann cell Merlin, with only a transient delay in myelination (2).

Recent studies have suggested that the mechanisms of PNS regeneration are distinct from normal development (4), so Parkinson and colleagues, led by postdoctoral researcher Thomas Mindos, then examined how their conditional knockout mice responded to peripheral nerve injury. Unlike wild-type animals, which can fully recover within three weeks, mice lacking Merlin failed to recuperate after their sciatic nerves were crushed, showing few signs of axonal regeneration or remyelination, even after several months (2).

Though Merlin-deficient Schwann cells lost their myelin after injury just like wild-type Schwann cells, they couldn't reprogram themselves to become repair-competent Büngner cells. They failed to normally up-regulate a critical transcription factor called cJun, and were therefore unable to induce production of neurotrophins such as GDNF and artemin. The cells remained highly proliferative and produced increased amounts of the inflammatory cytokine MCP-1, causing excessive recruitment of macrophages to the site of nerve damage. "So the loss of Merlin turns what should be an encouraging environment for regeneration into a pretty hostile, inflammatory environment," Parkinson says.

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One of the signaling pathways regulated by Merlin is the Hippo pathway, which inhibits the transcriptional coactivator YAP. Mindos et al. found that YAP levels were elevated in Merlin-deficient mice after nerve injury, whereas they remained unchanged in wild-type animals. "So we made double knockout mice lacking both Merlin and YAP and the animals functionally recovered almost perfectly after sciatic nerve injury," Parkinson says. Loss of YAP rescued most of the regeneration defects caused by Merlin deficiency; the formation of Büngner cells expressing cJun and neurotrophins was restored, whereas Schwann cell proliferation, expression of MCP-1, and the recruitment of macrophages were all reduced, allowing axons to regrow and remyelinate after injury.

Further experiments revealed that cJun expression is regulated by Merlin–YAP signaling, and Parkinson and colleagues are now searching for additional transcriptional targets of the pathway, as well as investigating the function of YAP's cofactor TAZ. The group's findings could have important therapeutic implications. PNS repair can be very slow in humans, particularly in older people or patients with peripheral neuropathies. Targeting the Merlin–YAP pathway might boost the regenerative process so that it can be completed while neuronal targets are still receptive to reinnervation. Moreover, some evidence suggests that peripheral nerve injury can initiate tumorigenesis (5), and Parkinson and colleagues are interested in whether the proinflammatory environment produced by elevated YAP activity might be responsible for this.

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