

 NERVE REGENERATION

A dual role for reactive astrocytes

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Although the ability of the adult mammalian CNS to regenerate is poor, temporary functional recovery is often observed soon after spinal cord injury (SCI). The mechanism underlying this phenomenon is unclear. Writing in *Nature Medicine*, Okada and colleagues show that astrocytic responses are important for tissue repair and recovery of motor function following injury.

In the injured CNS, reactive astrocytes form dense scar tissues — the glial scar — around the lesion site, and this serves to compact inflammatory cells and re-seal the blood–brain barrier after it has been broken by injury. To regenerating axons, the glial scar is bad news and represents an insurmountable molecular and physical barrier. In mice, the glial scar is formed around 14 days after

SCI, which coincides with the peak of functional improvement.

Do the initial astrocytic responses have a role in functional recovery in the early phase following injury? To address this issue, the researchers generated mice with defective astrocytic responses. The mice had selective deletion of either *Stat3* (signal transducer and activator of transcription 3) or its inhibitor *Soc3* (suppressor of cytokine signalling 3) in reactive astrocytes. STAT3 is thought to mediate a variety of biological processes, such as wound healing and cellular migration, and is a downstream effector molecule of several cytokines involved in regulating astrogliosis.

Okada *et al.* show that, in normal mice, phosphorylation (and therefore activation) of STAT3 in the spinal cord was markedly increased 12 hours after injury, and remained detectable for the following 2 weeks. In *Stat3*^{-/-} mice, scar-like tissue started to develop a few days after injury. However, a large proportion of astrocytes failed to migrate towards and accumulate around the lesion centre. As a result, the configuration of that tissue did not change significantly for the following 6 weeks, resulting in widespread infiltration of inflammatory cells, demyelination and severe motor deficits. The injury-induced loss of astrocytes was comparable in normal and *Stat3*^{-/-} mice, indicating that the lack of astrocyte accumulation at the lesion site was not due to reduced cell survival.

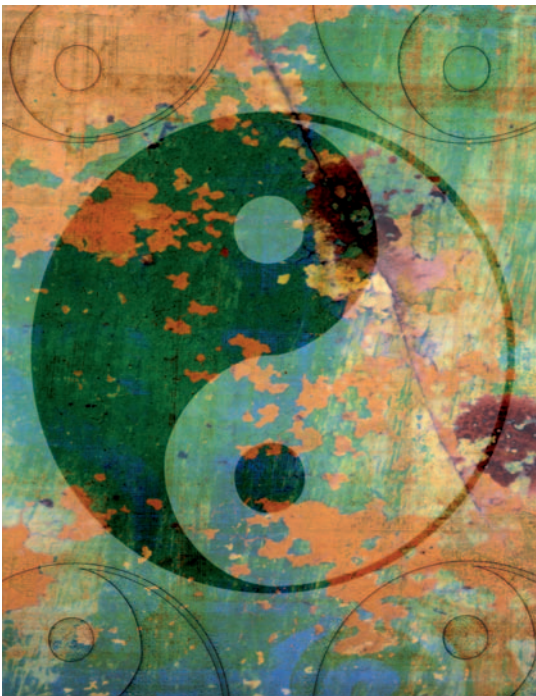
In *Soc3*^{-/-} mice, phosphorylation of STAT3 in the spinal cord after injury was much greater and more prolonged than that in wild-type animals. The astrocytic responses and glial scar formation were so

rapid that compacted inflammatory cells appeared as early as 7 days after injury. Compared to their wild-type counterparts, *Soc3*^{-/-} mice had less severe demyelination and oligodendrocyte loss, and more distal cord serotonergic innervation. They also showed more marked and persistent improvement of motor function.

To dissect the molecular mechanisms underlying the effects of STAT3 and SOC3 on astrogliosis, the researchers studied the migration behaviour of astrocytes in the *in vitro* scratch-wound assay, which simulates the injured spinal cord. Compared with their normal equivalents, astrocytes from *Stat3*^{-/-} mice showed impaired migration, whereas those from *Soc3*^{-/-} mice were more mobile. These changes in migration behaviour were associated with altered expression of E-cadherin and the zinc transporter LIV1 — a downstream target of STAT3.

The results show that reactive astrocytes are crucial for tissue repair and the initial functional recovery after SCI, which is largely mediated by STAT3 signalling. As the severed axons are unlikely to regenerate and reinnervate their target tissues within 2 weeks after injury, the nature and mechanism of the improved motor function remain to be seen.

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ORIGINAL RESEARCH PAPER Okada, S. *et al.* Conditional ablation of *Stat3* or *Soc3* discloses a dual role for reactive astrocytes after spinal cord injury. *Nature Med.* 18 June 2006 (doi:10.1038/nrn1425)

FURTHER READING Yiu, G. & He, Z. Glial inhibition of CNS axon regeneration. *Nature Rev. Neurosci.* 7, 617–627 (2006)

WEB SITE

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