

 NERVE REGENERATION

A strain on regeneration

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One of the key factors that blocks axonal regrowth following injury to the mature CNS is Nogo-A, a protein that is highly expressed in adult CNS myelin and inhibits neurite growth. In new work reported in *The Journal of Neuroscience*, Martin Schwab and colleagues showed surprising variability between two strains of Nogo-A-deficient mice in the extent of regeneration following corticospinal tract injury, which was attributable to differences in the expression of genes related to neurite outgrowth and synapse formation.

Preventing the action of Nogo-A by using neutralizing antibodies or by blocking the Nogo-A receptor subunit NgR in mature rodents permits considerable regrowth of damaged spinal cord fibre tracts and leads to restoration of function. However, there have been mixed findings from studies of Nogo-A-knockout mice, with some, but not all, reporting regeneration, despite using the same cell types and strains of mice — that is, chimeric mice generated from 129X1/SvJ embryonic stem cells that were implanted into C57BL/6 blastocytes.

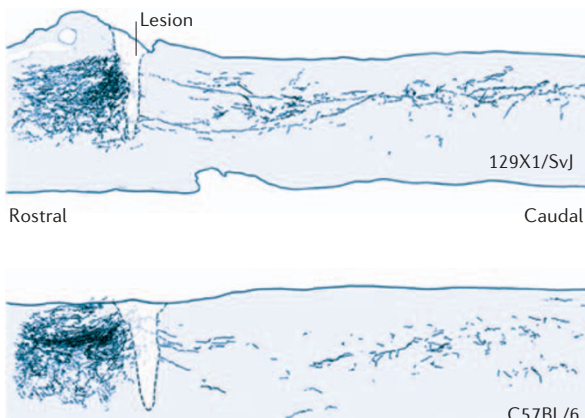
In these studies, the fraction of 129X1/SvJ and C57BL/6 genetic background in the different mouse lines was not determined, and it could be that genetic differences explain the conflicting findings between studies. Schwab and his team investigated this possibility by creating Nogo-A-specific knockouts in pure 129X1/SvJ and C57BL/6 strains of adult mice. In both strains, there was significant regrowth of axons of the corticospinal tract following partial transection compared with wild-type mice of the same strains. However, in 129X1/SvJ Nogo-A-knockout mice the number of fibres below the lesion was two to four times greater, and neurite

growth was significantly more pronounced, compared with C57BL/6 Nogo-A-knockout mice.

Microarray analyses of injured and non-injured tissue revealed important genetic differences between the two strains that might account for the disparity in potential for regeneration. Specifically, there was considerably greater expression of a number of genes that are related to neurite outgrowth, axon guidance, cell adhesion and synapse formation in 129X1/SvJ mice.

This work provides compelling evidence for the restorative effects of preventing Nogo-A action following CNS injury. Moreover, the data highlight the importance of the contribution of different genetic backgrounds to the potential for functional recovery, which should be considered when interpreting findings on nerve regeneration.

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Corticospinal axons were labelled with a tracer (biotin dextran amine) injection into the motor cortex following lesions to the spinal cord. Camera lucida drawings of a series of consecutive collapsed parasagittal sections of the lower thoracic spinal cord including the lesion site (light grey) show significantly more regeneration in 129X1/SvJ Nogo-A-knockout mice than in C57BL/6 Nogo-A-knockout mice. Image courtesy of M. E. Schwab, University of Zurich, Switzerland.

ORIGINAL RESEARCH PAPER Dimou, L. & Schnell, L. *et al.* Nogo-A-deficient mice reveal strain-dependent differences in axonal regeneration. *J. Neurosci.* **26**, 5591–5603 (2006)
FURTHER READING Yiu, G. & He, Z. Glial inhibition of CNS axon regeneration. *Nature Rev. Neurosci.* **7**, 615–625 (2006)