

LETTER TO THE EDITOR

Is inhibition of axonal regeneration by astrocytes, in the dorsal part of the spinal cord, regulated by p75 receptor?

Ti-Fei Yuan

NCI, China

Correspondence to: Ti-Fei Yuan,
NCI. E-mail: ytf0707@126.com

Sir, In a recent *Brain* paper by Scott and Ramer (2010), they provided intriguing evidence that p75 neurotrophin receptor deletion caused enhanced axonal regeneration in a mouse model of dorsal rhizotomy. They also reported improved functional recovery in p75 knockout mice and co-culture studies, suggesting that p75 receptor expressed on Schwann cells is an inhibitive factor for neurite outgrowth of dorsal root ganglion cells. Here, we would like to point out another potential factor that could lead to the enhanced axonal regeneration in p75 knockout mice: the reduced formation of glial scar by astrocytes following interruption of p75 signalling pathways.

In their model of axonal regeneration, the successfully regenerated axons penetrated the peripheral nervous system:central nervous system interface, and the local glial scar region formed after the dorsal rhizotomy. We acknowledge the function of Schwann cells in supporting axonal growth in the peripheral nervous system, especially myelination (Cosgaya *et al.*, 2002); however, once the axonal growth cones entered the central nervous system, astrocytes became the major inhibitive cellular component in the local environment. It was discovered that under brain injury conditions, astrocytes proliferate to form the glial scar, the process of which is correlated with up-regulated expression of p75 on astrocytes (Hanbury *et al.*, 2002; Oderfeld-Nowak *et al.*, 2003). It is highly possible that p75 knockout thus led to the reduction of reactive astrocytes following injury (Cragnolini and Friedman, 2008), contributing to the enhanced axonal regeneration. Consistent with this hypothesis, the author showed that in wild-type mice, most axons terminated at the peripheral nervous system:central nervous system interface, suggesting that the failure in axonal elongation across the astrocyte glial scar could be an important factor in their model.

Additionally, the proposal that inactivation of p75 neurotrophin receptor on Schwann cells during spinal cord injury recovery is too early. It has been found that p75 signalling is critical for

axonal remyelination in the peripheral part of axon regeneration; and p75 knockout mice showed thinner myelin after axonal regeneration (Cosgaya *et al.*, 2002; Tomita *et al.*, 2007), which is mediated via the brain-derived neurotrophic factor signalling pathway (Zhang *et al.*, 2000; Song *et al.*, 2006). It will be interesting to see if improved functional recovery occurs with decreased myelination in the peripheral nervous system.

References

- Cosgaya JM, Chan JR, Shooter EM. The neurotrophin receptor p75NTR as a positive modulator of myelination. *Science* 2002; 298: 1245–8.
- Cragnolini AB, Friedman WJ. The function of p75NTR in glia. *Trends Neurosci* 2008; 31: 99–104.
- Hanbury R, Charles V, Chen EY, Leventhal L, Rosenstein JM, Mufson EJ, et al. Excitotoxic and metabolic damage to the rodent striatum: role of the P75 neurotrophin receptor and glial progenitors. *J Comp Neurol* 2002; 444: 291–305.
- Oderfeld-Nowak B, Orzylowska-Sliwinska O, Soltys Z, Zaremba M, Januszewski S, Janeczko K, et al. Concomitant up-regulation of astroglial high and low affinity nerve growth factor receptors in the CA1 hippocampal area following global transient cerebral ischemia in rat. *Neuroscience* 2003; 120: 31–40.
- Scott AL, Ramer MS. Schwann cell p75NTR prevents spontaneous sensory reinnervation of the adult spinal cord. *Brain* 2010; 133: 421–32.
- Song XY, Zhou FH, Zhong JH, Wu LL, Zhou XF. Knockout of p75(NTR) impairs re-myelination of injured sciatic nerve in mice. *J Neurochem* 2006; 96: 833–42.
- Tomita K, Kubo T, Matsuda K, Fujiwara T, Yano K, Winograd JM, et al. The neurotrophin receptor p75NTR in Schwann cells is implicated in remyelination and motor recovery after peripheral nerve injury. *Glia* 2007; 55: 1199–208.
- Zhang JY, Luo XG, Xian CJ, Liu ZH, Zhou XF. Endogenous BDNF is required for myelination and regeneration of injured sciatic nerve in rodents. *Eur J Neurosci* 2000; 12: 4171–80.