



● EDITORIAL COMMENTARY

The astrocyte scar – not so inhibitory after all?

Damaged adult central nervous system axons have very limited regenerative capacity, if any. Other than an intrinsic deficiency (Liu et al., 2011) in axonal extension and guidance compared to embryonic neurons or peripheral neurons, the injury site is also generally viewed to be non-permissive for axonal regrowth. In particular, the formation of an astroglial scar with reactive astrogliosis (Cregg et al., 2014) is thought to generate both a physical and biochemical barrier against axonal regeneration. The latter activity appears to stem largely from glial associated inhibitors such as surface or secreted chondroitin sulfate proteoglycans (CSPGs), whose enzymatic removal was proven to enhance regeneration in animal models (Moon et al., 2001). This altogether rather dogmatic view has been a mainstay in the field of CNS regeneration, and much research in enhancing CNS regeneration has focused on attempts to alleviate glial inhibition.

Are the glial scar and the astrocytic CSPGs the absolute reasons for the lack of CNS axonal growth? The data accumulated over the years may appear rather overwhelming in favor of the notion. However, there were reports that suggest this view may be too simplistic. The Gage lab, for example, has shown that reactive astrocytes could support the growth of adult CNS axons in the presence of neurotrophins (Kawaja and Gage, 1991). The glial scar and reactive astrocytes are important local responses in CNS injury, and at the very least the former serves to confine neuroinflammation to the site of injury. Astrocytes are also known to secrete protective factors that enhance the survival of spare neurons (White and Jakeman, 2008). Now, a report from the Sofroniew lab has turned the table somewhat on the dogma of glial scar and reactive astrocyte inhibition of CNS axonal regeneration (Anderson et al., 2016).

The authors pointedly addressed the role of astrocytic scar and reactive astrocytes in axonal regeneration upon spinal cord injury (SCI) lesions using three genetic ablation approaches. In the first set of experiments, astrocytic scar formation was blocked by two separate methods, *via* selective ablation of proliferative reactive astrocytes (by a transgenic thymidine kinase/ganciclovir-mediated killing) or *via* shutting off the key signaling pathway in astrocyte activation (by GFAP-Cre mediated deletion of floxed STAT3 in astrocytes). Induction of crush SCI generated dense astrocytic scars in control animals, but the

genetically manipulated ones are essentially free of scar formation. Despite the absence of scars, axons of major cortical spinal tracts did not regrow through the lesioned area, and the descending corticospinal tract (CST) and ascending sensory tract (AST) axons in fact exhibited a significantly increased degree of axonal dieback compared to controls. Thus, the astrocytic scar appears to be dispensable for the inhibition of axonal regrowth through the lesion area.

If preventing scar formation in fresh injury sites failed to facilitate axonal regeneration of dying neurons in the midst of a massive neuroinflammatory response, will regeneration be enhanced if an already formed scar is removed from an old lesion where inflammation has since subsided, and the neurons are perhaps in a better shape to regenerate? The authors asked this question by removing chronic astrocytic scars five weeks after SCI injury with targeted expression of diphtheria toxin receptor and administration of very low doses of the toxin. Preformed scars were effectively ablated. However, once again the corticospinal tract axons all failed to regrow through the scar depleted areas.

In exploring the biochemical basis of axonal growth inhibition by comparing the control and the genetically manipulated animals, the authors made two interesting and important findings. The first is that CSPGs, which were elevated by SCI, were not significantly reduced by the disruption of scar formation. This indicates that reactive astrocytes may not be the major, and certainly not the only producer of growth inhibiting CSPGs. Secondly, transcription profiling of the lesions cites indicate a host of changes in the levels of a diverse mix of transcripts that are axonal growth inhibitory, as well as those that are growth promoting. In fact, both the scar-forming astrocytes and non-astrocytes in the lesion site upregulated several growth permissive molecules, such as laminin. There appears therefore to be no basis to believe that inhibitory molecules of axonal regeneration are specifically and exclusively upregulated at lesion sites.

That the axons failed to regenerate despite an absence of glial scar and reactive astrocytes could be down to their intrinsic inability to regenerate. Regeneration may, however, be enhanced by neurotrophins (Kawaja and Gage, 1991; Goldberg et al., 2002), and by preconditioning injuries (Ylera et al., 2009). The authors showed that preconditioning lesions of the sciatic nerve and the neurotrophins NT3 or BDNF delivered using hydrogel depots promoted fairly robust AST axonal regrowth through the astrocytic scars. Remarkably, this regrowth is not aided by the elimination of the astrocytic scar, but was in fact significantly attenuated by the absence of scars. The inevitable inference one might draw from this latter result is that



scar formation helps, rather than inhibits, AST axonal regeneration.

How does one reconcile these current findings with the prevailing dogmatic view that astrocytic scars are barriers and inhibitors of axonal regeneration? Of course, the experiments need to be expended to examine other CNS neuron types before we could be sure that the lesion scar is in fact a more benign entity than previously perceived in as far as CNS axonal regeneration is concerned. Previous lessons learned from the discrepancies in results from different manipulations and different laboratories working on the myelin-associated inhibitors have indicated that the genetic background of mice strains, as well as unknown or unpredictable background effects due to genetic manipulations, may play a role in regeneration outcome and measures (Teng and Tang, 2005). The precise cellular and tissue nature of the scarless lesion site needs to be better defined, with cell types and extracellular matrix molecules characterized. If these scarless sites are indeed more inhibitory to axonal growth than scar tissues, a better understanding of its molecular nature would be useful.

Any reservations aside, one could probably attempt to rationalize some the current findings from two aspects. The first of these pertained to astrocytic factors that could perhaps be axonal growth promoting rather than inhibitory. Astroglia secreted periostatin, for example, was recently shown to promote axonal regrowth and to overcome lesioned site inhibition (Shih et al., 2014). It is conceivable that other such factors will be identified in the near future. Secondly, other than serving a confinement role for the localized inflammatory response at the site of injury, the astrocytic scar may perhaps also be more a protective physical structure than previously envisioned. The authors' analyses revealed changes in the expressions of both growth promoting and growth inhibitory genes. The scar tissue, while not directly axonal growth promoting, may well be on the whole relatively more conducive than non-scarred tissue in maintaining the integrity of the proximal parts of the lesioned axon, and may in yet unknown ways delay or attenuate axonal dieback and Wallerian-type degeneration. While the notion of astroglia scar-based tissue being conducive for axonal regrowth remains rather unfathomable at the moment, it may be instructive to keep in mind that olfactory ensheathing glia has precisely such an architectural or scaffolding benefit for regenerating CNS axons (Roet and Verhaagen, 2014). The report by Sofroniew and colleagues has indeed opened up new avenues for exploration in the field of CNS regeneration.

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