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NEURAL REPAIR

Not such a scar on regrowth

> These findings indicate that the prevention of scar formation does not promote CNS axon regrowth in this SCI model

In the mature mammalian CNS, axons do not regrow following neuronal injury, and the release of factors from astrocytic scars — accumulations of reactive astrocytes at the injury site — is thought to contribute to the inhibition of this regrowth. However, a new study challenges this view by showing that, under certain conditions, such scars facilitate damaged axon regeneration.

The authors first examined whether preventing astrocytic scar formation affects axon regrowth in two types of adult transgenic mice that were subjected to a severe crush spinal cord injury (SCI). In one of these lines, scar-forming astrocytes were selectively killed (TK+GCV mice), whereas in the other line, STAT3 (signal transducer and activator of transcription 3) signalling was blocked specifically in astrocytes, inhibiting their proliferation and thus scar formation (STAT3-CKO mice).

Wild-type mice showed astrocytic scarring 2 weeks after SCI. By contrast, TK+GCV mice and STAT3-CKO mice did not exhibit scars. Interestingly, however, all three mouse types showed an absence of axonal regrowth in the three tracts assessed — the descending corticospinal tract, the ascending sensory tract (AST) and the descending serotonergic tract. These findings indicate that the prevention of scar formation does not promote CNS axon regrowth in this SCI model.

Next, the authors tested whether the removal of chronic scars affected axon regrowth. They subjected transgenic mice expressing diphtheria toxin receptor in astrocytes to SCI and then 5 weeks later gave them low doses of diphtheria to kill the reactive astrocytes. An analysis at 10 weeks post injury revealed no regrowth of axons in any of the aforementioned tracts, in line with the previous result.

Chondroitin sulfate proteoglycans (CSPGs) are considered to be major inhibitors of axon regeneration after injury, and astrocytic scars are thought to be the main source of these molecules. However, although the area of glial fibrillary acidic protein reactivity — a marker of astrocytes — at the site of injury was reduced in TK+GCV mice and STAT3-CKO mice compared with wild-type mice, all three types of mice showed similar areas of CSPG reactivity at injury sites, suggesting that other cells can be major sources of these molecules and that removing scars has little effect on total CSPG levels.

Previous studies showed that some AST axons can show regrowth if intrinsic regrowth programmes are activated through peripheral conditioning injuries and if cell grafts are present. These cell grafts provide not only a supportive matrix to grow on but also neurotrophin 3 (NT3) and brain-derived neurotrophic factor (BDNF), which act as growth cues for AST axons during development. The authors noticed that both neuropeptides were absent from wild-type SCI lesions and examined what effect peripheral conditioning plus the addition of these factors had on regrowth in the presence and absence of astrocytic scars. Strikingly, in wild-type mice, axons showed considerable AST axon regrowth through astrocytic scars under these conditions. By contrast, STAT3-CKO mice and TK+GCV mice showed little or no axon regrowth.

Together, these data suggest that axon scar formation does not prevent the regrowth of transected CNS axons but rather, under certain conditions, facilitates such regrowth.

Darran Yates

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