

Minireview

Bridging spinal cord injuries

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Abstract

One strategy for spinal cord injury repair is to make cellular bridges that support axon regeneration. However, the bridging cells often fail to integrate with host tissue and may lead to increased pain sensitivity. Recent work has tested bridging with two forms of progenitor-derived astrocyte. One type integrates, suppresses scar formation and promotes axon regeneration, whereas another very similar type, reported in *Journal of Biology*, does not support regeneration and increases pain sensitivity.

Repair of the injured spinal cord has been one of the great quests of experimental neuroscience since Tello and Cajal first showed in 1903 that axons in the central nervous system (CNS) can be made to regenerate. Sadly, we have yet to achieve a treatment that is licensed for this purpose in human patients, although advances such as that described by Davies *et al.* in this issue of the *Journal of Biology* [1] will help to bring this goal closer.

One of the earliest concepts in spinal cord repair was to build a bridge across the injury that would provide a road along which regenerating axons could cross the injury site to find suitable targets, form connections and restore function. This was first attempted by Peter Richardson, Sam David and Albert Aguayo in 1981 [2,3], when they implanted grafts of peripheral nerve tissue (which is permissive to axon regeneration) across a spinal injury. These experiments demonstrated both the possibilities and the problems of the bridging concept. Axons regenerated into the grafts, but only from nearby neurons, and hardly any of the axons could then leave the attractive environment of the graft to re-enter CNS tissue. In terms of bridge design, axons could traverse the on-ramp to get into the graft and they could grow across the bridge, but they got stuck on the off-ramp. What was the problem? The first was

that the Schwann cells - the supporting glial cells of the peripheral nervous system (PNS) - exert a honey-pot effect; growing axons are very good at selecting pathways and they will seldom grow from a permissive PNS environment to a less permissive CNS one. The second was that Schwann cells will not mix with astrocytes (the CNS glial cells), so a sharp cellular boundary of astrocytes reacting to the Schwann cells blocks the off-ramp.

Clearly, if the bridge concept is to work, we need to find a better type of cell with which to construct the bridge. This cell type must integrate seamlessly into spinal cord tissue, it must not stimulate a glial scar reaction and it must promote axon growth but not be so attractive that axons cannot pass on into the cord. Various cell types have been grafted into the spinal cord in the hope that they would have these properties, one of the most successful being olfactory ensheathing glia [4]. In this issue of *Journal of Biology*, Stephen Davies and co-workers [1] describe a particular type of immature astrocyte that seems to provide a very successful bridging material.

The idea of using embryonic CNS tissue and embryonic astrocytes for repairing the spinal cord has a long history. Axons grow in the embryonic CNS, so why not transplant

embryonic spinal cord into injuries? Host axons regenerate into these transplants, but seldom through them. In the grafts they can connect to graft neurons, which in turn can send their axons back into the host cord, the grafts acting as relays [5]. If embryonic CNS tissue promotes growth, then transplantation of embryonic glia is a logical next step, and there are reports going back to 1990 using this strategy to promote axon regeneration [6].

However, astrocytes are hugely diverse, some types being permissive to regeneration, others inhibitory. We now know much more about the various subtypes of glia and their developmental profiles, so it is possible to be more specific about which type of glial cell to transplant, and it is this knowledge that has formed the basis for the work from Davies and colleagues [1], who used immature glial precursor cells whose differentiation they manipulated *in vitro*. Various types of glial stem cell have been tried in earlier experiments, with mixed effects in the injured spinal cord. The transplants may protect the cord from secondary degeneration after injury and may produce myelinating cells, but they have not been very effective at promoting regeneration [7,8]. Indeed, Lars Olson and colleagues [9] report that stem cell transplants can stimulate sprouting of sensory axons leading to allodynia - a condition in which normal sensory stimuli cause pain.

In an earlier paper [10], Stephen Davies and collaborators reported the identification of a type of immature precursor-derived astrocyte that provides an excellent building material for spinal cord bridges, produced by treating glial-restricted precursors with bone morphogenetic protein (BMP)-4. The cells migrate into host tissue and mix with host glia while suppressing scar formation, and they promote regeneration of sensory axons and improved locomotor function. It will be interesting to compare these cells with the radial glial cells transplanted by the Grumet lab, which also had beneficial effects [11], and to see whether they promote the regeneration of motor pathways.

Davies and colleagues now report [1] the identification of a form of astrocyte, derived from exactly the same precursor population as used previously [10], that integrates poorly, does not stimulate regeneration or recovery and, worse still, induces allodynia by increasing sprouting of pain fibers in the dorsal horn of the spinal cord. These astrocytes were produced by treating the precursors with ciliary neurotrophic factor (CNTF) and have many of the properties of the 'type 2' astrocyte identified in glial cultures. This is important progress because grafts of embryonic or undifferentiated cells might be expected to produce both the good and bad types of astrocyte, and it emphasizes that small differences between closely related cells can be

associated with very different potentials for CNS repair. In this context it is interesting that infusing a CNTF-neutralizing antibody into a spinal cord containing transplanted neural stem cells reduced scarring and improved the outcome [12].

The finding by Davies and colleagues [1] and in a previous publication from the Olson lab [9] that a graft of the wrong type of glial cells can produce allodynia is particularly worrying. A third or more of spinal injury patients have intractable and continuous pain following their injury, which in some cases never responds satisfactorily to treatment. Spinal injury researchers worry that treatments that promote axon regeneration might also cause sprouting of pain fibers, making pain worse. Treating the injured spinal cord with nerve growth factor (NGF) can do this because pain fibers express the NGF receptor *trkA* [13], but the finding that glial transplants can cause a pain syndrome is a shock. It is not clear from either paper [1,9] why this might have happened, but Davies and colleagues [1] suggest that activation of microglia might be involved.

If progenitor-derived astrocytes produced by BMP-4 treatment are the cells we need in spinal cord injuries, how are we to get them there? In this paper [1] the cells were derived from spinal cord taken from rats at embryonic day 13.5. Can they be derived from embryonic stem cells, or from induced pluripotent state cells taken from the patient? Or are there glial precursors in the injured cord that could be induced to produce the right cell type? There will also have to be a decision on whether the progenitor-derived astrocyte is a more or less effective bridging cell than the olfactory ensheathing cell. From a practical point of view, cells derived in some way from individual patients will avoid the need for immunosuppression. However, such autologous cells will not be available until some time after injury, and it will be important to know for how long after damage the transplants remain effective. Current work has involved transplantation at the time of injury, which will be difficult to achieve in human patients.

There are several treatments under development for spinal cord injury, aimed at various mechanisms, including neutralization of inhibitory molecules, promotion of plasticity, direct stimulation of axon regeneration, bridging and control of inflammation. A combination of two or more of these approaches will be needed to achieve optimal spinal cord repair. So far there have been relatively few attempts at combination treatments, mainly because most of the individual treatments have not been fully optimized and because spinal repair experiments involving many experimental groups are very demanding. The work from Davies and collaborators [1] and other groups in identifying an optimized cell type for grafting into injuries is very

welcome, and it should provide a transplant strategy that can be combined with other treatments.

What do these findings mean for patients with spinal cord injuries? Unfortunately they do not lead immediately to a treatment applicable to injured humans. However, grafting cells into injuries to suppress scarring and provide a bridge will be an important component of a successful combinatorial treatment, and the findings reported by Davies and colleagues [1] bring safe and efficacious grafts appreciably closer.

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