stem cell research&therapy

COMMENTARY

The fate of proliferating cells in the injured adult spinal cord

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Abstract

Endogenous cell proliferation and gliogenesis have been extensively documented in spinal cord injury, particularly in terms of proliferating oligodendrocyte progenitor cells. Despite the characterization of different proliferating cell types in the intact and injured spinal cord, the exact sources of new glial cells have remained elusive. Most studies on cell fate within the spinal cord have focused on following the progeny of one specific population of dividing cells, thus making it difficult to understand the relative contributions of each mitotic cell population to the formation of new glia after spinal cord injury. A recent study from the Frisen laboratory is the first to quantitatively and qualitatively characterize the response of ependymal cells, oligodendrocyte progenitors, and astrocytes in parallel by using transgenic reporter mice corresponding to each cell type. The investigators characterize the distribution and phenotype of progeny, along with the quantitative contributions of each progenitor type to newly formed cells. Their findings provide valuable insight into the endogenous cell replacement response to spinal cord injury, thus paving the way for advances in modulating specific populations of progenitor cells with the goal of promoting structural and functional recovery after spinal cord injury.

Over the last several decades, determining the extent to which endogenous cells within the spinal cord can replace neurons and glia that are lost following spinal cord injury (SCI) has generated increasing interest. While it is known that neurogenesis occurs regularly in certain regions of the adult brain, this process has not been identified within the adult spinal cord. Interestingly, this is likely to be a factor of the spinal cord microenvironment because cells isolated from adult spinal cords can generate neurons, oligodendrocytes, and astrocytes both *in vitro* and when transplanted into a neurogenic region of the brain [1]. What clearly does occur after SCI is marked gliogenesis [2-5]. SCI leads to significant and protracted proliferation of endogenous cells, which contribute to the replacement of oligodendrocytes and astrocytes. Indeed, the oligodendrocytes formed along the lesion borders significantly outnumber those found in naïve tissue, revealing that the spontaneous oligogenic potential of the adult spinal cord is quite robust [2].

The source of the new glia after SCI has been more difficult to nail down. In the uninjured adult spinal cord, there are two major populations of dividing cells: the slowly dividing ependymal cells surrounding the central canal and the NG2$^+$ glial progenitors distributed throughout the gray and white matter. Much work has been done to track the fate of NG2$^+$ progenitors after SCI, and reports suggest that *in vivo* they contribute to robust oligodendrocyte replacement and potentially make some new astrocytes [2,3,5]. Studies have also used cell lineage mapping or specific markers to track the fate of dividing ependymal cells after injury; these studies suggest that ependymal cells proliferate after SCI, migrate away from the central canal, and differentiate into new astrocytes [6-9]. A final possible source of new cells after SCI is mature astrocytes, which divide after injury and thereby increase overall astrocyte numbers.

Most of these studies, though informative, have been limited by the types of cells that could be followed over time and have focused mainly on the progeny of one single population of dividing cells. Thus, it has been difficult to discern the relative contributions of each dividing cell population to the formation of new glia after SCI. A recent study from the Frisen laboratory attempted for the first time to quantitatively and qualitatively compare the response of all three proliferating cell types after SCI [10]. The investigators achieved this by performing dorsal spinal hemisections in three different tamoxifen-dependent Cre recombinase (CreER) reporter mice under the control of nonoverlapping promoters highly

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specific to each of the cell types. The FoxJ1 promoter was used to delineate ependymal cells, connexin 30 promoter to delineate astrocytes, and Olig2 promoter to label oligodendrocyte lineage cells. The investigators thoroughly characterized the recombination frequencies and the phenotypes of recombinant cells for each mouse line prior to SCI and then characterized the distribution and number of progeny from each population at different times post-injury.

The Barnabe-Heider report confirms work by others that $NG2^+$ oligodendrocyte progenitor cells (OPCs) display the highest level of baseline proliferation in uninjured condition. However, despite their dominance in noninjury conditions and increased proliferation after SCI, OPCs come in third place for net cell contribution after SCI. At 2 weeks post-injury, the period in which the astrocytic glial scar is being established, astrocyte duplication is the main type of cell renewal, with ependymal cells also contributing a substantial 30% to new astrocytes. At more chronic times, ependymal cells give rise to more than half of newly formed astrocytes. Therefore, it appears that ependymal cells and astrocytes demonstrate similarly robust astrocytic properties subacutely and chronically after injury, and this is also consistent with previous reports [7,8,11]. These findings also demonstrate that astrocytes and OPCs are restricted to their own lineage phenotype after injury whereas ependymal cells display bipotential differentiation *in vivo*. This contrasts somewhat with a previous study, which used a retrovirus expressing green fluorescent protein (GFP) under the NG2 promoter and which suggested that cycling $NG2^+$ progenitors give rise to astrocytes, at least very early after dorsal hemisections [5]. The Frisen study examined more chronic times post-injury and therefore gives insight into the NG2 cell progeny that survive long-term.

Thus, their study provides important information on the relative contributions of different pools of cells in the adult spinal cord to cell replacement after injury. It also defines the final distribution of the cell progeny, with ependymal-derived astrocytes mostly within the lesion, astrocyte-derived astrocytes forming the lesion borders, and OPC-derived and, to a lesser extent, ependymal-derived new oligodendrocytes present in spared tissue surrounding the lesion. A fruitful line of future investigation may be to determine ways in which to enhance ependymal-derived oligogenesis, which may aid in remyelination after SCI and eliminate the need for transplanting exogenous cells.

A potential limitation of this study in terms of clinical relevance is the use of a dorsal hemisection model, which is rarely seen clinically. Instead, most patients with SCI sustain a contusion-type trauma, which results in a central cavitating lesion surrounded by a rim of surviving but dysfunctional tissue. In these injuries, the central canal is usually destroyed at the injury site, and this would mean that the potential for ependymal cells to contribute to cell replacement may be restricted to the lesion poles rather than the epicenter region. It will be very interesting to see whether the Frisen laboratory or others perform similar fate mapping studies using spinal contusion models next.

Abbreviations

OPC, oligodendrocyte progenitor cell; SCI, spinal cord injury.

Competing interests

The authors declare that they have no competing interests.

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