Spinal cord injury is followed by glial scar formation, which has positive and negative effects on recovery from the lesion. More than half of the astrocytes in the glial scar are generated by ependymal cells, the neural stem cells in the spinal cord. We recently demonstrated that the neural stem cell–derived scar component has several beneficial functions, including restricting tissue damage and neural loss after spinal cord injury. This finding identifies endogenous neural stem cells as a potential therapeutic target for treatment of spinal cord injury.

Figure 1. Generation and Distribution of Cells After Spinal Cord Injury

A, Type A pericytes (orange) around the vessel wall divide, leave the vessel wall, and generate stromal cells after spinal cord injury. Resident astrocytes (red) divide and become reactive after spinal cord injury. Ependymal neural stem cells (green) divide, leave the central canal region, and generate both astrocytes and oligodendrocytes after spinal cord injury. B, Type A pericyte progeny generates stromal cells forming the fibrotic scar in the core of the lesion (orange). Resident astrocytes contribute to the outer portion of the glial scar (red). Ependymal neural stem cell progeny generates both remyelinating oligodendrocytes in the parenchyma and astrocytes in the inner portion of the glial scar (green).
Spinal Cord Injury and Scar Formation

Spinal cord injury leads to massive cell death and disruption of the blood–spinal cord barrier, followed by infiltration of immune cells. Inflammation, free radical formation, and other cellular events at the lesion site cause a secondary injury cascade that kills additional cells, including oligodendrocytes that myelinate axons of surviving neurons.\(^5\) Demyelinated axons are vulnerable to degeneration; without rapid remyelination, the neurons may die, resulting in worsened damage and functional impairment.\(^6\)

Neural Stem Cells’ Role in Spinal Cord Injury

Ependymal cells are ciliated cells lining the ventricular system of the brain and the central canal of the spinal cord. They are responsible for propulsion of cerebrospinal fluid and function as a barrier to the brain and spinal cord parenchyma.\(^5\) In the intact spinal cord, ependymal cells rarely divide, but in cell culture they start dividing vigorously and demonstrate multipotency by giving rise to astrocytes, oligodendrocytes, and neurons.\(^8\) In vivo after spinal cord injury, ependymal cells start dividing rapidly and generate more than half the astrocytes in the glial scar and a small amount of oligodendrocytes that myelinate axons (Figure 1).\(^1\)

Oligodendrocyte progenitor cells also generate mature oligodendrocytes. Oligodendrocyte progenitor cells are the main dividing cell population in the intact adult spinal cord, and they increase their rate of division after spinal cord injury and generate large numbers of remyelinating oligodendrocytes.\(^8\) Astrocytes divide sporadically in the intact spinal cord to maintain their population. After injury, astrocytes become reactive, divide rapidly, and form the border of the glial scar (Figure 1).\(^8,9\) Astrocytes and oligodendrocyte progenitor cells self-renew but are not multipotent, which indicates that they are not stem cells.\(^8\) However, ependymal cells display neural stem cell properties in culture and after spinal cord injury by generating new ependymal cells as well as astrocytes and oligodendrocytes. Therefore, ependymal cells represent a latent neural stem cell population in the adult spinal cord.\(^8\)

The scar formed after spinal cord injury was long seen mainly as a physical barrier preventing axonal regeneration. Glial scar astrocytes produce inhibitory factors, such as chondroitin sulfate proteoglycans, that prevent axons from growing through the scar.\(^9\) However, the view of the scar has become more nuanced as numerous beneficial functions of the scar have been reported. Astrocytes in the glial scar have been killed or inactivated in several studies to shed light on their functions. Ablating astrocytes in the glial scar may affect infiltration of immune cells and lead to larger lesion volume, increased neuronal death, and worsened functional outcome, suggesting beneficial effects of glial scar astrocytes on the outcome after spinal cord injury. However, the glial scar is generated by different cell types, which produce scar components with detrimental and/or beneficial effects on recovery.\(^7,9\) Since previous studies targeted scar-forming astrocytes produced by self-duplicating astrocytes and neural stem cells, it has been difficult to draw any definite conclusions about the function of each separate scar component.

To study specific functions of the neural stem cell-derived glial scar component, our laboratory generated mice with an inducible knockout of all Ras genes.\(^10\) The Ras gene knockout rendered the endogenous neural stem cells unable to proliferate, and consequently, the neural stem cell-derived component of the glial scar...
was never formed. Large cysts developed at the lesions when the proliferation of neural stem cells was blocked, while no cyst formation occurred in mice with normal neural stem cell function. This outcome implies that neural stem cell progeny functions as a scaffold within the scar to restrict secondary enlargement of the lesion and prevents the lesion from expanding after the initial insult. Indeed, spinal cord injuries in mice without the scar component from neural stem cells grew progressively deeper over time and severed additional axonal tracts after the initial insult (Figure 2). There was also an increased loss of neurons after spinal cord injury in mice without neural stem cell progeny formation (Figure 2). Neural stem cell progeny was found to be necessary for production of several neurotrophic factors that support neuronal survival after insults in the central nervous system. The increased loss of neurons was attributed to the loss of neurotrophic support from neural stem cell progeny.10

Conclusions

Neural stem cells are a source of glial scar astrocytes with beneficial functions, including preserving tissue integrity and supplying neurotrophic support for surviving neurons. The beneficial effects of endogenous neural stem cells after spinal cord injury highlight them as a potential therapeutic target. It is important to investigate the identity, potential, and regulation of endogenous neural stem cells to successfully modulate their injury response. Interesting venues to explore include increasing neural stem cell progeny formation and redirecting neural stem cells to produce more oligodendrocytes after spinal cord injury. To improve recovery from spinal cord injury by modulating the scar, it is essential to examine the specific role of resident astrocytes in scar formation and the interactions between astrocyte-derived and neural stem cell–derived scar components.