Neural Stem Cell Dissemination after Grafting to CNS Injury Sites

Steward and colleagues report that implants of E14 rat spinal-cord-derived multipotent neural progenitor cells are associated with ectopic deposits of cells, occasionally at long distances from a T3 spinal cord lesion and grafting site. Of 20 grafted rats, half showed ectopic cell deposits. One rat had a deposit of cells in the 4th ventricle, from which relatively few axons extended into the tegmentum. Half of animals had cells within six spinal segments of the lesion site, and of these, three had deposits more distantly.

There is a long and well-established precedent for the finding that neural stem cells and other nervous system cells can spread over extended distances through the adult nervous system (Fricker et al., 1999, Li et al., 2003, Han et al., 2004, Guzman et al., 2007, Pearse et al., 2007, Goldman et al., 2012). Previous reports have also specifically documented spread of implanted cells through the central canal and subpial region (Li et al., 2003, Pearse et al., 2007). Re-examination of specimens from our original report (Lu et al., 2012) confirms that ectopic cell deposits were found in three of six animals with complete transections. A few points should be noted in interpreting findings specific to our experiment and the letter of Steward et al. (2014).

First, in our experiment and that of Steward et al., injections into the lesion cavity in rats were made using a PicoSpritzer (General Valve), which generates pulses of relatively high pressure (in excess of 1,000 mm Hg). For comparison, human blood pressure typically reaches a peak systolic pressure of 120 mm Hg. This high pressure would tend to force cells from the lesion site and cause remote cell dissemination (Lu et al., 2006, Pearse et al., 2007). Lower pressure injections might be associated with lower risk. Indeed, in nonhuman primates (rhesus monkeys) our grafting technique into C7 spinal cord lesion sites uses a low pressure grafting method and ectopic cell deposits have not been detected in any of six monkeys as of this date (E.S. Rosenzweig, et al., 2013, Soc. Neurosci. abstracts).

Second, in moving from rat to primate studies, we have increased the concentrations of fibrinogen and thrombin in the grafting mixture, resulting in more rapid gelling and lower potential risk of cells escaping from the lesion site.

Third, humans have a "vestigial" central canal that becomes functionally closed in most individuals by the second decade of life (Milhorat et al., 1994). Thus, the risk of cell spread through this cavity may be reduced in humans. However, humans with posttraumatic syrinx formation might be at greater risk of remote cell migration through a patent central canal.

Fourth, these were syngeneic grafts of E14 spinal cord donor tissue, analogous from an immunologic perspective to cell autografts in humans. Systematic study of migratory properties of neural stem cells or multipotent neural progenitor cells from other donor cell types and across outbred individuals is required to fully appreciate whether cells will distribute ectopically after grafting, particularly when using human cells.

Fifth, cells in rats with complete transections were injected into an open spinal canal with direct access to the cerebrospinal fluid. In contrast, humans typically have contusion-type injuries with a closed lesion cavity surrounded by an outer perimeter of white matter. We envision that cells would be injected into this type of cavity, were this approach to be translated to human trials. Hence, the chance of broad cell dissemination in the spinal fluid might be reduced. Experiments are currently underway grafting cells into a closed contusion cavity in rats.

Caution is prudent in generalizing findings from a single cell type, a single lesion model, and a unique high-pressure injection system, to all approaches that utilize neural stem cells. We consider the most notable feature of neural stem cell biology, relayed in our report (Lu et al., 2012), to be the astonishing ability of multipotent neural progenitor cells to extend axons in high numbers and over very long distances through the injured adult spinal cord. This suggests many fruitful avenues for further investigation, including studies focused on both mechanism and translation. Adequate safety and biodistribution studies should always be performed prior to initiation of human clinical trials using neural stem cells for any indication.

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