HHS Public Access

Author manuscript

J Neurosci Res. Author manuscript; available in PMC 2019 August 01.

Published in final edited form as:

J Neurosci Res. 2019 February ; 97(2): 109–111. doi:10.1002/jnr.24351.

Choosing the right cell for spinal cord repair

Lyandysha V. Zholudeva[1,2] and **Michael A. Lane**[1,2]

[1]Department of Neurobiology and Anatomy, College of Medicine, Drexel University, Philadelphia, Pennsylvania

[2]The Spinal Cord Research Center, College of Medicine, Drexel University, Philadelphia, Pennsylvania

Keywords

interneurons; spinal cord; spinal cord injury; transplantation

There is a rich history of neural progenitor transplantation for repair of the injured central nervous system (Anderson, Howland, & Reier, 1995; Bonner & Steward, 2015; Jakeman & Reier, 2015; Lane, Lepore, & Fischer, 2017; Lu, 2017; Nori, Nakamura, & Okano, 2017; Tetzlaff et al., 2011). Sugar and Gerard (1940) were among the first to transplant developing spinal cord tissue into the injured adult spinal cord to facilitate repair, albeit with limited efficacy. In the 1980's Reier and colleagues at the University of Florida extended this work to show that transplantation of embryonic spinal cord tissues promoted repair and functional recovery following experimental spinal cord injury (SCI) in mice, rats, and cats (Reier et al., 2002). This work was eventually then translated for a small clinical study in patients undergoing surgery for post-traumatic syringomyelia—the first study of its kind in people with SCI (Reier, 2004; Thompson et al., 2001; Wirth et al., 2001). This prompted subsequent studies that transplanted stem cell derived neural precursor cells into the injured spinal cord, and led to the first FDA approved stem cell trial in the United States.

Initial studies by Reier and colleagues also began to characterize the cytoarchitecture of transplanted tissue to determine how transplanted tissues were able to promote repair and restore tissue continuity (Eng, Reier, & Houle, 1987; Giovanini, Reier, Eskin, Wirth, & Anderson, 1997; Horner, Reier, & Stokes, 1996; Jakeman et al., 1989; Stokes & Reier, 1991; White et al., 2010). The transplanted tissue was shown to produce a heterogeneous mix of mature neurons and glia, become vascularized (Giovanini et al., 1997; Horner et al., 1996), and retained its capacity to produce spinal cord morphology (Jakeman et al., 1989; White et al., 2010) as it matured within the injury site. Within donor neurons alone there is a vast range of spinal interneuronal precursors that have wide ranging excitatory, modulatory, or inhibitory functions. Small, tightly packed populations of donor neurons that are morphologically comparable to the substantia gelatinosa of the mature dorsal horn (Jakeman

Correspondence: Lyandysha V. Zholudeva, Department of Neurobiology & Anatomy, Drexel University, 2900 W Queen Lane, Philadelphia, PA 19129. lvzholudeva@gmail.com.

CONFLICT OF INTEREST

None to declare.

et al., 1989; White et al., 2010), have been found to be derived from the dorsal (alar) region of the developing spinal cord (White et al., 2010). Donor cells from this region have since also been shown to be innervated by the appropriate host cell axons over time (Dulin et al., 2018). Donor tissues derived from the developing ventral (basal) spinal cord resulted in quite unique donor morphology, with higher levels of myelin (White et al., 2010). However, with this heterogeneity comes the caveat that not all donor components are beneficial for functional improvement, and some recovery may in fact be limited if the wrong donor source is used (White et al., 2010). With this in mind, there has been a growing interest in interneuronal phenotypes that exist within donor tissues, and which may be optimal for transplantation.

Building on the early studies transplanting developing spinal cord tissues, Fischer and colleagues at Drexel University extended this work to culture embryonically derived spinal tissues to select for neuronal and glial restricted progenitors (excluding extracellular matrix and vascular endothelial cells, among other cellular components). Like the tissue transplants, cultured neural progenitors restored tissue continuity and enhanced repair. But an important consideration is that preparing tissue in this more clinically relevant way may also alter their developing neuronal phenotype (Zholudeva, Iyer, et al., 2018a).

Spinal interneurons (SpINs) and their roles in the development of neural circuits, as well as their neuroplastic and therapeutic potential following SCI and disease, are of growing interest within the neurosciences (Zholudeva, Qiang, et al., 2018b). Ventrally derived developing spinal cord is typically considered to comprise neurons with motor functions, while dorsal tissue is more closely associated with sensory functions (Lu, Niu, & Alaynick, 2015). For this reason, and due to the potentially more limited efficacy seen with transplantation of dorsally derived donor tissues, there is growing interest in ventrally-derived phenotypes for spinal cord repair (Brock, Graham, Staufenberg, Im, & Tuszynski, 2018; Spruance et al., 2018; Zholudeva, Iyer, et al., 2018a).

The cover image shows developing rat spinal cord tissue (embryonic day 13.5) that has been transplanted into the injured adult rat spinal cord. The image was taken from a histological section collected through the donor tissue, 3 days after transplantation. This transplanted tissue is rich with developing spinal interneurons (SpINs), which are key cellular elements for neuroplasticity after injury. One subtype of SpINs—the V2a SpINs—is immunohistochemically labeled with a transcriptional factor Chx10 (red), while nestin (green) stains immature neural tissue. This image was inspired by the explosion in research of V2a SpINs in neural development, plasticity and repair, and our hypothesis that these cells could be one of the beneficial elements for repair. The V2a SpINs have gained attention as an excitatory, pre-motor interneuron that might contribute to improved motor function in pre-clinical models of injury (traumatic SCI) or disease (amyotrophic lateral sclerosis; ALS), and can be generated from stem cell populations (Butts et al., 2017; Iyer, Huettner, Butts, Brown, & Sakiyama-Elbert, 2016). They have been shown to contribute to anatomical (Zholudeva, Karliner, Dougherty, & Lane, 2017) and functional (Romer et al., 2016) plasticity in respiratory neural circuits and play a role in locomotor central pattern generator circuits (Dougherty & Kiehn, 2010; Hayashi et al., 2018). More recently, we have shown that enriching donor cells with stem cell derived V2a interneurons can enhance the extent of

motor recovery within an anatomically and functionally defined spinal network—the phrenic motor system (Zholudeva, Iyer, et al., 2018a).

Future work will now be able to build upon this work to more extensively characterize the phenotype of SpINs, and even other donor cell types. Such research will significantly advance on previous transplantation studies, and help to determine optimal donor cells for spinal cord repair.

CAPTION

The cover image is of developing rat spinal cord-derived tissue (embryonic day 13.5) 3 days after it has been transplanted into an injured adult rat spinal cord. The injury in this case was a cervical level spinal contusion. This transplanted tissue is rich with developing spinal interneurons (SpINs), which have been shown to be key cellular elements for neuroplasticity after injury. One particular subtype—the V2a SpINs—is immunohistochemically labeled with a transcriptional factor Chx10 (red), while nestin (green) stains immature neural tissue. These cells have been shown to play an important role in neuroplasticity of both respiratory and locomotor circuits after injury or disease and may represent an important therapeutic target.

Acknowledgments

Funding information

This work was funded by the NINDS, NIH R01 NS081112 (Lane), ROl NS104291 (Lane), The Moseley Foundation (Lane), Craig H. Neilsen #338432 (Lane), the Drexel Deans Fellowship for Collaborative or Themed Research (Zholudeva), and the Spinal Cord Research Center at Drexel University, College of Medicine (Lane)

REFERENCES

Anderson DK, Howland DR, & Reier PJ (1995). Fetal neural grafts and repair of the injured spinal cord. Brain Pathology, 5(4), 451–457. https://doi.org/10.llll/j.1750-3639.1995.tb00624.x [PubMed: 8974628]

Bonner JF, & Steward O (2015). Repair of spinal cord injury with neuronal relays: From fetal grafts to neural stem cells. Brain Research, 1619, 115–123. 10.1016/j.brainres.2015.01.006 [PubMed: 25591483]

Brock JH, Graham L, Staufenberg E, Im S, STuszynski MH (2018). Rodent neural progenitor cells support functional recovery after cervical spinal cord contusion. Journal of Neurotrauma, 35(9), 1069–1078. 10.1089/neu.2017.5244 [PubMed: 29279015]

Butts JC, McCreedy DA, Martinez-Vargas JA, Mendoza-Camacho FN, Hookway TA, Gifford CA, … McDevitt TC (2017). Differentiation of V2a interneurons from human pluripotent stem cells. Proceedings of the National Academy of Sciences of the United States of America, 114(19), 4969–4974. 10.1073/pnas.1608254114 [PubMed: 28438991]

Dougherty KJ, & Kiehn O (2010). Firing and cellular properties of V2a interneurons in the rodent spinal cord. The Journal of Neuroscience: The Official Journal of the Society for Neuroscience, 30(1), 24–37. 10.1523/JNEUROSCI.4821-09.2010 [PubMed: 20053884]

Dulin JN, Adler AF, Kumamaru H, Poplawski GHD, Lee-Kubli C, Strobl H, … Tuszynski MH (2018). Injured adult motor and sensory axons regenerate into appropriate organotypic domains of neural progenitor grafts. Nature Communications, 9(1), 84 10.1038/s41467-017-02613-x

Eng LF, Reier PJ, & Houle JD (1987). Astrocyte activation and fibrous gliosis: Glial fibrillary acidic protein immunostaining of astrocytes following intraspinal cord grafting of fetal CNS tissue. Progress in Brain Research, 71, 439–455. [PubMed: 3588961]

Giovanini MA, Reier PJ, Eskin TA, Wirth E, & Anderson DK (1997). Characteristics of human fetal spinal cord grafts in the adult rat spinal cord: Influences of lesion and grafting conditions. Experimental Neuroiogy, 148(2), 523–543. 10.1006/exnr.1997.6703

Hayashi M, Hinckley CA, Driscoll SP, Moore NJ, Levine AJ, Hilde KL, … Pfaff SL (2018). Graded arrays of spinal and supraspinal V2a interneuron subtypes underlie forelimb and hindlimb motor control. Neuron, 97(4), 869–884, e865. 10.1016/j.neuron.2018.01.023 [PubMed: 29398364]

Horner PJ, Reier PJ, & Stokes BT (1996). Quantitative analysis of vascularization and cytochrome oxidase following fetal transplantation in the contused rat spinal cord. The Journal of Comparative Neurology, 364(4), 690–703. 10.1002/(SICI)1096-9861(19960122)364:4<690:AID-CNE7>3.0.CO;2-Z [PubMed: 8821455]

Iyer NR, Huettner JE, Butts JC, Brown CR, & Sakiyama-Elbert SE (2016). Generation of highly enriched V2a interneurons from mouse embryonic stem cells. Experimental Neurology, 277, 305–316. 10.1016/j.expneurol.2016.01.011 [PubMed: 26784005]

Jakeman L, & Reier P (2015). Fetal spinal cord transplantation after spinal cord injury: Around and back again In So K-F & Xu X-M (Eds.), Neural regeneration (pp. 351–368). London, UK; Beijing, Germany: Academic Press is an imprint of Elsevier; Academic Press Beijing.

Jakeman LB, Reier PJ, Bregman BS, Wade EB, Dailey M, Kastner RJ, … Tessler A (1989). Differentiation of substantia gelatinosa-like regions in intraspinal and intracerebral transplants of embryonic spinal cord tissue in the rat. Experimental Neurology, 103(1), 17–33. 10.1016/0014-4886(89)90181-7 [PubMed: 2912747]

Lane MA, Lepore AC, & Fischer I (2017). Improving the therapeutic efficacy of neural progenitor cell transplantation following spinal cord injury. Expert Review of Neurotherapeutics, 17(5), 433–440. 10.1080/14737175.2017.1270206 [PubMed: 27927055]

Lu P (2017). Stem cell transplantation for spinal cord injury repair. Progress in Brain Research, 231, 1–32. [PubMed: 28554393]

Lu DC, Niu T, & Alaynick WA (2015). Molecular and cellular development of spinal cord locomotor circuitry. Front Mol Neurosci, 8, 25 10.3389/fnmol.2015.00025 [PubMed: 26136656]

Nori S, Nakamura M, & Okano H (2017). Plasticity and regeneration in the injured spinal cord after cell transplantation therapy. Progress in Brain Research, 231, 33–56. [PubMed: 28554400]

Reier PJ (2004). Cellular transplantation strategies for spinal cord injury and translational neurobiology. NeuroRx: The Journal of the American Society for Experimental NeuroTherapeutics, 1(4), 424–451. 10.1602/neurorx.l.4.424 [PubMed: 15717046]

Reier PJ, Golder FJ, Bolser DC, Hubscher C, Johnson R, Schrimsher GW, & Velardo MJ (2002). Gray matter repair in the cervical spinal cord. Progress in Brain Research, 137, 49–70. [PubMed: 12440359]

Romer SH, Seedle K, Turner SM, Li J, Baccei ML, & Crone SA (2016). Accessory respiratory muscles enhance ventilation in ALS model mice and are activated by excitatory V2a neurons. Experimental Neurology, 287(Pt 2): 192–204. [PubMed: 27456268]

Spruance VM, Zholudeva LV, Hormigo KM, Randelman ML, Bezdudnaya T, Marchenko V, & Lane MA (2018). Integration of transplanted neural precursors with the injured cervical spinal cord. Journal of Neurotrauma, 10.1089/neu.2017.5451

Stokes BT, & Reier PJ (1991). Oxygen transport in intraspinal fetal grafts: Graft-host relations. Experimental Neurology, 111(3), 312–323. [PubMed: 1999233]

Sugar O, & Gerard RW (1940). Spinal cord regeneration in the rat. Journal of Neurophysiology, 3(4), 1–19. 10.1152/jn.1940.3.1.1

Tetzlaff W, Okon EB, Karimi-Abdolrezaee S, Hill CE, Sparling JS, Plemel JR, … Kwon BK (2011). A systematic review of cellular transplantation therapies for spinal cord injury. Journal of Neurotrauma, 28(8), 1611–1682. 10.1089/neu.2009.1177 [PubMed: 20146557]

Thompson FJ, Reier PJ, Uthman B, Mott S, Fessler RG, Behrman A, … Wirth E (2001). Neurophysiological assessment of the feasibility and safety of neural tissue transplantation in patients with syringomyelia. Journal of Neurotrauma, 18(9), 931–945. 10.1089/089771501750451848 [PubMed: 11565604]

White TE, Lane MA, Sandhu MS, O'Steen BE, Fuller DD, & Reier PJ (2010). Neuronal progenitor transplantation and respiratory outcomes following upper cervical spinal cord injury in adult rats. Experimental Neurology, 225(1), 231–236. 10.1016/j.expneurol.2010.06.006 [PubMed: 20599981]

Wirth ED, 3rd, Reier PJ, Fessler RG, Thompson FJ, Uthman B, Behrman A, … Anderson DK (2001). Feasibility and safety of neural tissue transplantation in patients with syringomyelia. Journal of Neurotrauma, 18(9), 911–929. 10.1089/089771501750451839 [PubMed: 11565603]

Zholudeva LV, Iyer NR, Qiang L, Spruance VM, Randelman ML, White NW, … Lane MA (2018a). Transplantation of neural progenitors and V2a interneurons after spinal cord injury. Journal of Neurotrauma.

Zholudeva LV, Karliner JS, Dougherty KJ, & Lane MA (2017). Anatomical recruitment of spinal V2a interneurons into phrenic motor circuitry after high cervical spinal cord injury. Journal of Neurotrauma, 34(21), 3058–3065. 10.1089/neu.2017.5045 [PubMed: 28548606]

Zholudeva LV, Qiang L, Marchenko V, Dougherty KJ, Sakiyama-Elbert SE, & Lane MA (2018b). The neuroplastic and therapeutic potential of spinal interneurons in the injured spinal cord. Trends in Neurosciences, 41(9), 625–639. [PubMed: 30017476]