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Review Article

Harnessing the power of cell transplantation to target respiratory dysfunction following spinal cord injury

Brittany A. Charsar, Mark W. Urban, Angelo C. Lepore *

Department of Neuroscience, Farber Institute for Neurosciences, Sidney Kimmel Medical College, Thomas Jefferson University, 900 Walnut Street, JHN 418, Philadelphia, PA, 19107, United States

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ABSTRACT

The therapeutic benefit of cell transplantation has been assessed in a host of central nervous system (CNS) diseases, including disorders of the spinal cord such as traumatic spinal cord injury (SCI). The promise of cell transplantation to preserve and/or restore normal function can be aimed at a variety of therapeutic mechanisms, including replacement of lost or damaged CNS cell types, promotion of axonal regeneration or sprouting, neuroprotection, immune response modulation, and delivery of gene products such as neurotrophic factors, amongst other possibilities. Despite significant work in the field of transplantation in models of SCI, limited attention has been directed at harnessing the therapeutic potential of cell grafting for preserving respiratory function after SCI, despite the critical role pulmonary compromise plays in patient outcome in this devastating disease. Here, we will review the limited number of studies that have demonstrated the therapeutic potential of intraspinal transplantation of a variety of cell types for addressing respiratory dysfunction in SCI.

Contents

Abbreviations: BDNF, brain-derived neurotrophic factor; BMNC, bone marrow nucleated cell; C2, 3, 4, etc., cervical level 2, 3, 4, etc.; ChABC, chondroitinase ABC; CMAP, compound muscle action potential; CNS, central nervous system; CPP, crossed phrenic phenomenon; CSPG, chondroitin sulfate proteoglycan; EMG, electromyography; ES cells, embryonic stem cells; FSC, fetal spinal cord; GAG, glycosaminoglycan; GLT1, glutamate transporter 1; GRP, glial-restricted precursor; iPS cell, induced Pluripotent Stem cell; MB cell, embryonic midline brainstem cell; MSC, mesenchymal stem cell; NMJ, neuromuscular junction; NPC, lineage-restricted neural progenitor cell; NSC, multipotent neural stem cell; OEC, olfactory ensheathing cell; PhMN, phrenic motor neuron; PNG, peripheral nerve graft; PNS, peripheral nervous system; PRV, pseudo-rabies virus; rVRG, rostral Ventral Respiratory Group; SCI, spinal cord injury; 5-HT, 5-hydroxytryptamine (serotonin).

* Corresponding author at: Department of Neuroscience, Farber Institute for Neurosciences, Sidney Kimmel Medical College, Thomas Jefferson University, 900 Walnut Street, JHN 418, Philadelphia, PA 19107, United States.
E-mail address: angelo.lepore@jefferson.edu (A.C. Lepore).

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1. Spinal cord injury

Spinal cord injury (SCI) represents a heterogeneous set of conditions resulting from trauma to the spinal cord. The specific collection of functional deficits after SCI depends on factors such as location, type, and severity of the traumatic event (McDonald and Becker, 2003). Greater than half of all SCI cases occur in the cervical region. Damage in this location can result in respiratory compromise that is physically and psychologically debilitating, because injury frequently disrupts the neural circuitry that controls critical muscles such as the diaphragm (Lane et al., 2008a). Even injuries at more caudal levels, such as those in the thoracic spinal cord, can result in significant and persistent pulmonary dysfunction, including compromised breathing and effects on critical non-ventilatory functions, like coughing (Warren and Alilain, 2014).

The pathophysiology of SCI is complex and multi-factorial due to both the variety of cell types and the complexity of the neuronal connections affected. However, this also provides a number of potential therapeutic mechanisms to target with transplantation (Goulao and Lepore, 2016) specifically in the context of respiratory dysfunction post-SCI. These mechanisms include the obvious but challenging replacement of injured long-distance projecting neurons of the circuits controlling breathing. To date, transplantation-based interventions have been used to promote plasticity of axonal connections that are part of these respiratory circuits (Alilain et al., 2011; Decherchi and Gauthier, 2002; Decherchi et al., 1996; Li et al., 2003; Polentes et al., 2004; Stamegna et al., 2011), replacement of glial cell types (Li et al., 2015a; Li et al., 2015b) and local respiratory interneurons (Lee et al., 2014; White et al., 2010) of the cervical spinal cord, delivery of neurotrophic factor support (Gransee et al., 2015), and restoration of neurotransmitter signaling (Dougherty et al., 2016; Li et al., 2015a; Li et al., 2015b). While this list only represents a few of the possible benefits that transplantation can provide, the fact that only a limited number of studies have to date been conducted in this field means that many of the potential mechanistic benefits of transplanted cells have yet to be explored for targeting respiratory dysfunction in SCI.

2. Promoting axonal regrowth

Regeneration of damaged axons and reconnection with appropriate post-synaptic structures is a major therapeutic goal for SCI treatment. In addition, promoting sprouting of damaged and/or spared fibers is another important and possibly more easily achievable goal, which would involve generation of novel connections that could underlie meaningful recovery of function (Bareyre et al., 2004). Unfortunately, a host of neuronal-intrinsic (Luo and Park, 2012) and environmental (Bradbury et al., 2002; Giger et al., 2010) factors limit or prevent robust axonal regrowth in CNS diseases such as SCI. A number of studies have used transplants to induce plasticity of axonal populations that are involved in controlling breathing (Alilain et al., 2011; Decherchi and Gauthier, 2002; Li et al., 2003; Polentes et al., 2004; Stamegna et al., 2011). The premise behind these approaches is that a variety of cell types, some of which are not derived from the CNS, appear to have properties that can promote robust axonal growth, even in the injured spinal cord.

Many of these studies focused on axonal regrowth targeting a specific neural circuit that is central to inspiration via diaphragmatic control (Fig. 1A). Each hemi-diaphragm is separately innervated by a pool of phrenic motor neurons (PhMNs) located at mid-cervical levels (Lane et al., 2009). These PhMNs are not spontaneously active; instead, they receive primarily monosynaptic drive from bulbospinal axonal input from neurons whose cell bodies are located ipsilaterally in a medullary nucleus called the rostral Ventral Respiratory Group (rVRG), in addition to some contralateral input from the crossed phrenic pathway (Boulenguez et al., 2007; Goshgarian et al., 1991; Lane et al., 2009). Cervical SCI can result in damage both to PhMNs and to descending rVRG connections to spared PhMNs (Zimmer et al., 2007). There is also growing appreciation for the important role that intraspinal respiratory interneuron populations play in diaphragm function (Lane et al., 2008b).

Several neuroanatomical mechanisms associated with restoration of this circuit have been targeted using cell transplantation to achieve recovery of diaphragm function in rodent models of unilateral cervical SCI. Though technically challenging due to intrinsic (Luo and Park, 2012) and extrinsic (Bartus et al., 2012) inhibitors of axonal growth, transplants could be used to promote regeneration of injured rVRG axons through and/or around the lesion and back toward PhMNs and/or local respiratory interneuron populations. Spared contralateral rVRG input has also been shown to be a potential substrate for diaphragm recovery - even spontaneously - through mechanisms that promote plasticity such as activation of latent contralateral rVRG synaptic input to denervated PhMNs located ipsilateral to the lesion (Warren et al., 2014). Futhermore, cell transplants could be used to activate latent connections from the crossed phrenic pathway by modulating synaptic transmission between contralateral rVRG fibers and PhMNs and/or by promoting actual sprouting of these contralateral rVRG axons toward the ipsilateral PhMN pool. Transplant cells may also have the capacity

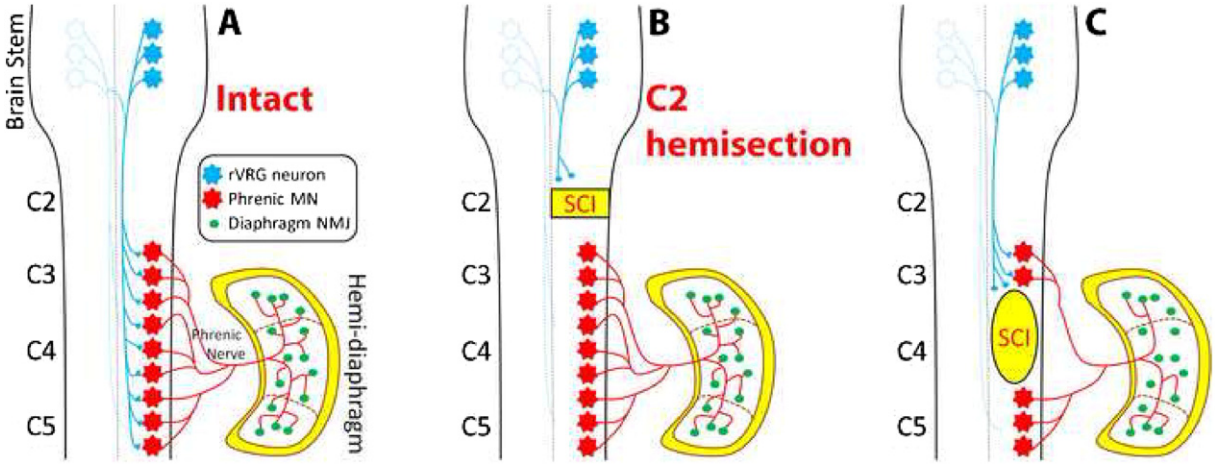

Fig. 1. Animal models of cervical SCI used to study diaphragm dysfunction. Intact rVRG-PhMN-diaphragm circuitry (A). C2 hemisection SCI (B). Unilateral C4 contusion SCI (C). Contralateral bulbospinal input is illustrated in light blue dashed lines in all panels. rVRG: rostral Ventral Respiratory Group. PhMN: phrenic motor neuron. NMJ: neuromuscular junction. SCI: spinal cord injury site. C2, C3, C4, C5: cervical spinal cord levels 2, 3, 4 and 5.