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PERSPECTIVES

Effect of microenvironment modulation on stem cell therapy for spinal cord injury pain

Spinal cord injury (SCI) currently ranks second after mental retardation among neurological disorders in terms of cost to society. Pain is a debilitating consequence of SCI related to the nature of the lesion, neurological structures damaged, and secondary pathophysiological changes of surviving tissues (Yezierski, 2005; D'Angelo et al., 2013). Approximately two-thirds of persons who have sustained SCI experience clinically significant pain after injury, of whom one-third have severe pain (Finnerup et al., 2001; Siddall et al., 2003). Post-SCI pain can increase with time and is often refractory to conventional treatment approaches (Rintala et al., 1998). Over the past decade, clinical studies have shown that post-SCI pain interferes with rehabilitation, daily activities, and quality of life and may substantially influence mood, leading to depression and even suicide (Segatore, 1994; Rintala et al., 1998; Westgren and Levi, 1998; Widerstrom-Noga et al., 2001).Chronic neuropathic pain following SCI is divided into three types: at-level pain (pain within the body segments innervated by spinal cord segments at the level of the injury), below-level pain (pain within body segments caudal to the level at which the spinal cord was injured), and above-level pain (pain within body segments rostral to the level at which the spinal cord was injured) (Waxman and Hains, 2006). The mechanisms underlying SCI-induced chronic neuropathic pain are not well understood. Aberrant central sprouting of nociceptive fibers has been commonly proposed as a mechanism of SCI pain and is associated with mechanical allodynia induced by SCI (Christensen and Hulsebosch, 1997; Yezierski, 2000; Finnerup and Jensen, 2004). Demyelination (loss of myelin) and dysmyelination (abnormal myelination) induced by oligodendrocyte injury and death are important contributors to SCI-associated behavioral deficits, including pain (Bunge et al., 1961; Blight, 1983; Bunge et al., 1993; Liu et al., 1997; Becker et al., 2003). For instance, SCI-induced dysmyelination is involved in the aberrant sprouting of nociceptive fibers and causes SCI pain behaviors. Thus, remyelination of demyelinated/dysmyelinated axons in the injured spinal cord could be an important repair therapy for SCI and one of the key elements for functional recovery and aberrant sprouting prevention after SCI (McDonald and Belegu, 2006; Plemel et al., 2014).

SCI pain is extremely debilitating and remains largely unmanageable by current therapeutic strategies. In the past decade, experimental studies on stem cell therapy for SCI-induced chronic neuropathic pain have emerged and sparked tremendous interest in this once obscure field. In preclinical research, predifferentiated ES cells prevented chronic pain behaviors and restored sensory function following SCI in mice (Hendricks et al., 2006), and subarachnoid transplant of a human γ-aminobutyric acid-secreting neuronal cell line, hNT2.17, attenuated chronic allodynia and hyperalgesia after excitotoxic SCI in rats (Eaton et al., 2007). However, grafting of neural stem cells (NSCs) caused aberrant axonal sprouting associated with allodynia-like forelimb hypersensitivity in a rat contusion SCI model (Hofstetter et al., 2005; Macias et al., 2006). In contrast, transduction of NSCs with neurogenin-2 before transplantation differentiated cells into oligodendrocytes and prevented graft-induced sprouting and allodynia. Moreover, the transduction with neurogenin-2 also improved the positive effects of engrafted stem cells, including increased amounts of myelin in the injured area and recovery of hind limb locomotor function and sensory responses (Hofstetter et al., 2005; Klein and Svendsen, 2005). These results suggest that increasing the production of oligodendrocytes reduces allodynia and improves functional recovery.

Given that a substantial cause of neurological deficits after SCI is oligodendrocyte death leading to demyelination and dysmyelination, the goal of stem cell transplantation should be guided to promote remyelination of spared axons in the injured spinal cord. It is now recognized that oligodendrocytes are important near-term clinical targets for restoring function after CNS injury, particularly SCI. Thus, directed differentiation of stem cells to oligodendrocyte precursors prior to transplantation may be an effective strategy to increase the extent of remyelination for the treatment of SCI. For remyelination, oligodendrocyte precursors must further differentiate into mature oligodendrocytes. However, the transplanted OPCs cannot survive for a long time and many of them cannot mature into myelinating oligodendrocytes. Previous studies have demonstrated that appropriate trophic modulation of the microenvironment in the injured spinal cord can promote oligodendroglial differentiation and maturation (Barres and Raff, 1994; Barres et al., 1994; Kumar et al., 1998; McTigue et al., 1998; Yan and Wood, 2000; Franklin et al., 2001; Cosgaya et al., 2002; Jean et al., 2003; Karimi-Abdolrezaee et al., 2012).

Neurotrophins [such as neurotrophin 3 (NT3) and brain-derived neurotrophic factor (BDNF)] play key roles in OPC proliferation and myelin formation. D15A is a multineurotrophin that binds to neurotrophin receptors trkB and trkC and has both BDNF and NT3 activities (Urfer et al., 1994; Strohmaier et al., 1996). NT3 and BDNF regulate neuronal development and axonal regeneration (Xu et al., 1995; Zhou and Shine, 2003). They are also important mediators of myelination. Mice that lack functional trkC or NT3 are deficient in both mature oligodendrocytes and OPCs (Kumar et al., 1998). NT3 enhances the survival and proliferation of OPCs *in vitro* (Barres and Raff, 1994; Kumar et al., 1998; Yan and Wood, 2000; Franklin et al., 2001) and *in vivo* (Barres et al., 1994). Myelination produced byoligodendrocytes is also enhanced by NT3 in cultured neurons and the injured CNS (McTigue et al., 1998; Yan and Wood, 2000; Jean et al., 2003). BDNF is known to be important for myelin formation during development because inactivation of BDNF signaling by deletion of trkB receptors causes myelin deficits both *in vivo* and *in vitro* (Cosgaya et al., 2002). Treatment with neurotrophins and glial-restricted precursor cell grafts promotes differentiation of oligodendrocyte lineage and facilitates functional recovery after traumatic SCI (Cao et al., 2005). Taken together, these results suggest that appropriate trophic modulation of the molecular microenvironment in the injured spinal cord can affect differentiation and maturation of transplanted stem cells and that the combination strategy with stem cell graft and microenvironment modulation can be used to enhance therapeutic efficacy of cell transplantation.

SCI is a serious clinical condition that results in persistent motor and sensory deficits. Patients with SCI, who often are injured at an early age, experience life-long alterations in quality of life. Functional deficits following SCI result from damage to axons, loss of neurons and glia, and demyelination/dysmyelination in the injured spinal cord (Totoiu and Keirstead, 2005). Thus, remyelination appears to be one of the most feasible restoration strategies for SCI treatment. Animal studies from our laboratory and others have shown that stem cell transplantation with OPCs could produce remyelination in the injured spinal cord and partially improve functional recovery after SCI (Liu et al., 2000; Keirstead et al., 2005; Nistor et al., 2005; Tao et al., 2013). However, the efficacy of the cell transplantation approach is not significantly sufficient due to the transplanted OPCs' short-term survival and their low maturation rate in the injured spinal cord. Therefore, future studies should be conducted to explore a novel approach by combining stem cell grafting with microenvironment modulation to enhance stem cell therapy for SCI and SCI-induced pain.

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