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Review

Cell-based transplantation strategies to promote plasticity following spinal cord injury

Crystal A. Ruff [a,1], Jared T. Wilcox [b,1], Michael G. Fehlings [a,b,c,*]

[a] Toronto Western Research Institute, Division of Genetics and Development, Toronto, Ontario, Canada
[b] University of Toronto, Institute of Medical Science, Toronto, Ontario, Canada
[c] University of Toronto, Department of Surgery, Toronto, Ontario, Canada

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ABSTRACT

Cell transplantation therapy holds potential for repair and functional plasticity following spinal cord injury (SCI). Stem and progenitor cells are capable of modifying the lesion environment, providing structural support and myelination and increasing neurotrophic factors for neuroprotection and endogenous activation. Through these effects, transplanted cells induce plasticity in the injured spinal cord by promoting axonal elongation and collateral sprouting, remyelination, synapse formation and reduced retrograde axonal degeneration. In light of these beneficial effects, cell transplantation could be combined with other treatment modalities, such as rehabilitation and immune modulation, to provide a synergistic functional benefit. This review will delineate 1) stem/progenitor cell types proposed for cell transplantation in SCI, 2) *in vitro* evidence of cell-induced mechanisms of plasticity, 3) promotion of functional recovery in animal models of SCI, 4) successful combinatorial strategies using cell transplantation. Current treatment modalities for SCI provide modest efficacy, especially in chronic stages of SCI. Hence, combinatorial stem cell transplantation strategies which could potentially directly address tissue sparing and neuroplasticity in chronic SCI show promise. Rigorous evaluation of combinatorial approaches using stem cell transplantation with appropriate preclinical animal models of SCI is needed to advance therapeutic strategies to the point where clinical trials are appropriate. Given the high patient demand for and clinical trial precedent of cell transplantation therapy, combination stem cell therapies have the promise to provide improved quality of life for individuals, with corresponding socioeconomic benefit.

Contents

* Corresponding author. Division of Genetics and Development, Toronto Western Research Institute, University Health Network, 399 Bathurst St. Toronto, Ontario, Canada M5T 2S8.
E-mail address: Michael.fehlings@uhn.on.ca (M.G. Fehlings).
[1] These authors contributed equally to this work.

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Introduction

Cell transplantation therapy holds the potential to promote repair and functional plasticity following spinal cord injury (SCI). Due to their pleiotrophic nature, stem cells have tremendous therapeutic promise, by using several different mechanisms that increase anatomic plasticity and sensorimotor recovery. Within this review, plasticity will be operationally defined as the adaptive reorganisation of connectivity through axonal regeneration, collateral sprouting, unmasking of existing synapses, and activation of ascending/descending pathways (Fig. 1). Factors promoting plasticity will refer to alterations that increase and permit anatomic plasticity through lesion modification and glial scar degradation, growth and survival promotion through trophic factors, and removal of inhibitory signalling. Functional recovery will indicate returns in the conductance and physiology of the spinal cord and improved motor and sensory functions based on repair factors.

The pathophysiology of SCI comprises a composite progression of well-characterised spatial and temporal alterations. Knowledge of these separate processes allows for specific therapeutic targeting (Fig. 1). Insult to the spinal cord is typically contusive with subsequent compression, resulting in the severing of axons and hypoxic sequelae due to ischemia. Edema, lipid peroxidation, inflammation and excitotoxicity cause oligodendroglial death and demyelination of surviving axons (Sekhon and Fehlings, 2001). Distal axons subsequently degenerate, with corollary proximal axons unable to grow through the glial scar due to inhibitory myelin fragments within the lesion site (Schwab, 2002; Fawcett, 2006). Approaches that address this to increase anatomic plasticity include the enzyme Chondroitinase ABC (ChABC) to degrade the gliotic scar and implanting scaffolds or olfactory ensheathing cells (OECs) to guide axons into and through the lesion (Busch and Silver, 2007; Rowland et al., 2008). Axonal regeneration and subsequent plasticity are further hindered due to deficient oligodendroglial regeneration (Li et al., 1996; Casha et al., 2001). Dysmyelination occurs and consists of disrupted myelin structure and improperly organised intranodal calcium and paranodal potassium channels, which greatly impedes axonal conduction (Nashmi et al., 2000; Nashmi and Fehlings, 2001; Karimi-Abdolrezaee et al., 2004). Cellular approaches to address dysmyelination include transplantation of neural stem/progenitor cells (NSPCs), oligodendrocyte precursors (OPCs) or Schwann cells (SCs) to directly remyelinate axons, or bone marrow stromal cells (BMSCs) and growth factor infusions to upregulate survival and activity of myelinating cells (Barnabé-Heider and Frisén, 2008; Rossi and Keirstead, 2009). Although SCs are not stem cells by definition, they possess plastic properties; they can revert between mature and immature phenotypes following injury (Parkinson et al., 2004, 2008; Jessen and Mirsky, 2010) and act as precursors to generate large numbers of mature offspring during life. They are, therefore, commonly used in cellular replacement strategies for SCI. Similarly, OECs, although not technically stem cells, are able to generate large pools of myelinating cells and show reversible morphological plasticity *in vitro* (Vincent et al., 2003, 2005; Radtke and Vogt, 2009) and have also been widely employed in cell transplantation paradigms; they will therefore also be discussed in this article. This review will address the potential benefits of OECs, SCs, BMSCs, NSPCs and pluripotent cells—in ascending order of self-renewal, potency and clinical utility—for neural plasticity and repair after SCI. Each pathologic process potentiates gliosis, cyst formation and vascular changes that remodel spinal tissue in the chronic phase of injury, creating an established inhibitory lesion (Sekhon and Fehlings, 2001). Addressing a chronic phase lesion will likely require a multifactorial approach including scar-degrading enzymes, trophic support, and cell replacement to promote remyelination (Bradbury and McMahon, 2006; Eftekharpour et al., 2008).

Development of new strategies to treat SCI is required since current treatment options are limited and, at best, provide only modest recovery. Modern advances in surgical interventions and management of injuries involving the spinal column and underlying cord have drastically reduced mortality rates and contributed to increased lifespan of SCI patients. Mortality from traumatic SCI has been reduced to less than half of the rates in the mid twentieth century; unfortunately, despite this increased survival patients with SCI continue to harbour significant morbidity (Sekhon and Fehlings, 2001; Krause et al., 2010). Moreover, clinical trials of pharmacologic therapeutics within the last two decades have either failed to prove efficacy (Geisler et al., 2001) or have provided only modest reductions in functional deficits (Bracken et al., 1990; Fehlings, 2001; Baptiste and Fehlings, 2007, 2008).

The clinical impact of SCI is further supported by epidemiological evidence, which suggests an annual incidence of 30–49 cases of traumatic (t)SCI per million in North America, with 10–29 cases per million throughout the rest of the developed world (Cripps et al., 2010). A recent study done jointly by the Rick Hansen Institute and the Urban Futures organisation puts this number as high as 52 tSCI cases per million in Canada, considering a population of 34 million (Farry and Baxter, 2010; Government of Canada, 2011). Moreover, an extensive and rigorous survey recently conducted by the Christopher and Dana Reeve Foundation (2010) suggests that roughly 1.2 million Americans live with some degree of paralysis caused by traumatic or non-traumatic SCI. The greatest incidence of tSCI in the developed world results from motor vehicle or vocation-associated accidents in the young, working age demographic (16–37 years), which creates substantial personal and socioeconomic costs; among ageing populations, falls are an increasing cause of tSCI (Christopher and Dana Reeve Foundation, 2010; Farry and Baxter, 2010; Cripps et al., 2010). The disease burden of SCI is further compounded by the fact that the majority of patients have chronic cervical injury. Indeed, the National Spinal Cord Injury Statistical Center (2009) estimates that each young individual acquiring high tetraplegia will accrue an additional associated lifetime costs of $3.1 million. New therapies directly addressing tissue sparing and neuroplasticity in chronic SCI must be pursued if morbidity and societal burdens are to be reduced.

Current treatment modalities are mostly ineffective for chronic SCI; however, modest recovery is seen with rehabilitation and pharmacologic agents for incomplete SCI (Baptiste and Fehlings, 2007). Contrary to previous assumption, the spinal cord exhibits robust spatiotemporal reorganisation following SCI in both human and non-human primate models (Grasso et al., 2004; Rosenzweig et al., 2010). More importantly, this modification of tracts and