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Review

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

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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

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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

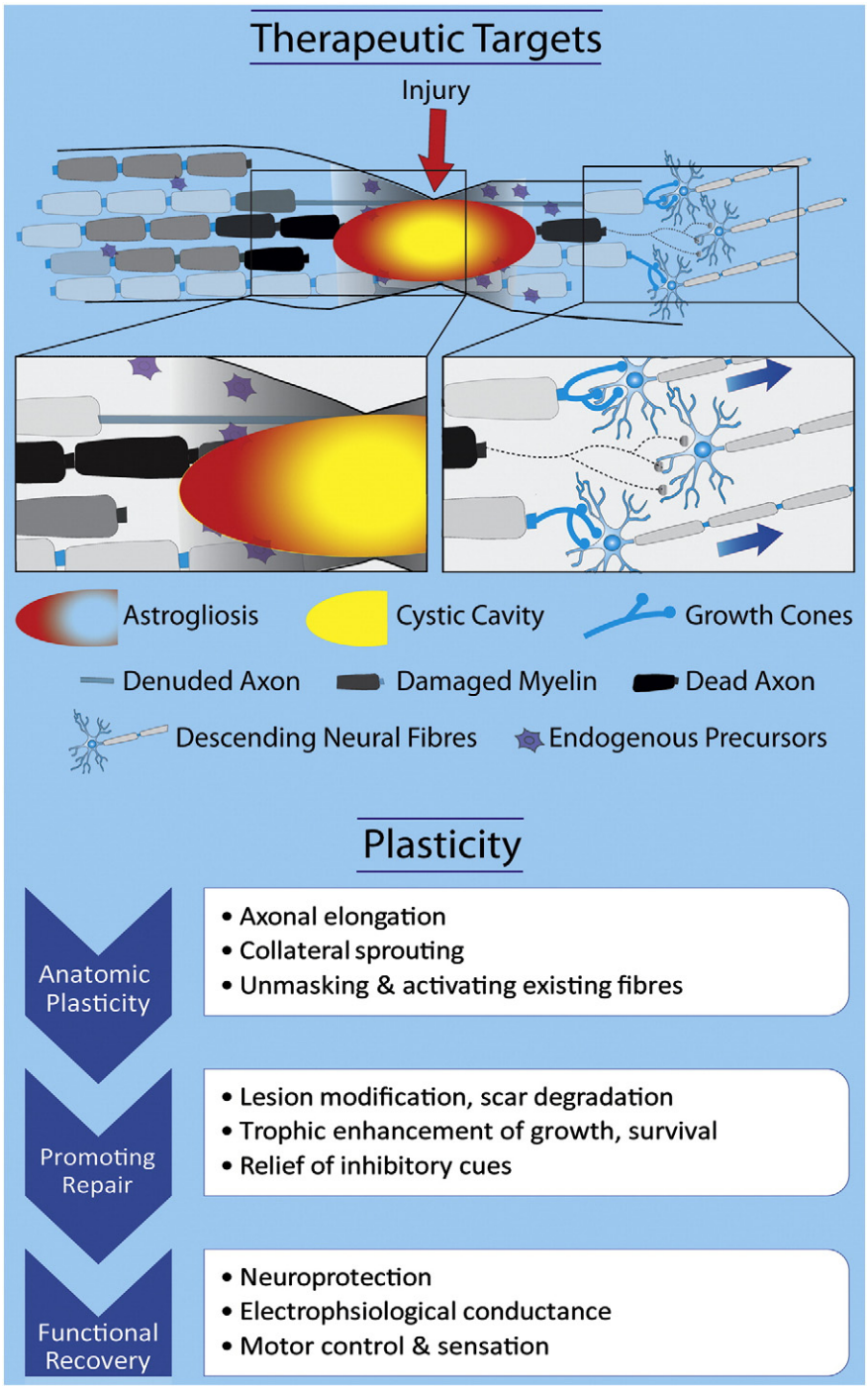

Fig. 1. Pathophysiology of SCI and mechanisms of plasticity. (Top) SCI is accompanied by excitotoxic and mechanically-induced cell death, with associated demyelination. At the site of injury, there exists cystic cavity formation and gliotic scar accumulation along the sub-pial rim. There is additional evidence that endogenous neural precursors can be recruited to penumbral regions. Sublesional connectivity is compromised, affecting both descending motor pathways and ascending sensory tracts. (Bottom) Connectivity is established through axonal elongation, collateral sprouting and unmasking or activation of existing sensorimotor tracts. This anatomical plasticity, which is enabled via these three key mechanisms, can lead to anatomical and functional benefits.

pattern generators occurs over the rostrocaudal extent of the cord, and in animal models, rehabilitation alone serves to activate endogenous spinal cord ependymal progenitor cells (Foret et al., 2010). The opportunity to enhance endogenous adaptability through cell-based approaches has led to a great interest in developing cell transplantation therapies that could potentiate and synergise with other treatment modalities to maximise neuroplasticity and produce meaningful recovery.

This review will address transplantation of stem and progenitor cells as part of a combinatorial strategy for SCI. We will first delineate the stem and progenitor cell types currently being evaluated in preclinical models in ascending order, considering both their potency, self-renewal and therapeutic potential. Characteristics and purported mechanisms of action of these cells will then be discussed, with specific attention paid to axonal regeneration and re-growth, growth factor release, guidance through inhibitory cues, remyelination and induction of anatomical neuroplasticity. These mechanisms will finally be evaluated through results in animal models, with *in vivo* demonstration of environmental modification, axonal density, myelin deposition, and functional recovery. Numerous permutations of injury

type, cell source, intervention time point, histological and neurobehavioral outcomes have been studied; however, they extend beyond the scope of this review—for a systematic review, see Tetzlaff et al. (2010).

Stem cells and other cells of interest for neural transplantation

Stem cells are pluripotent cells present in both developing and adult tissue. They are characterised by the extent of diverse cell types into which they can differentiate and possess unique properties, such as the capacity for asymmetric cell division and enhanced proliferative capacity. During development, particularly surrounding embryogenesis, cells have the potential to divide almost indefinitely, into the more than 290 distinct adult cell types. As an organism matures, pluripotency genes are down-regulated and with accompanying changes in epigenetic profile, cells lose their pluripotency. Although some stem cells remain in adult tissue, the majority of somatic cells are incapable of further differentiation, with most neurons remaining post-mitotic.

Bone marrow stromal cells (BMSCs)

Perhaps the most widely applied stem cells in human transplantation are bone marrow-derived mesenchymal stem cells. Bone marrow stromal cells (BMSCs), a subfraction of which are potent mesenchymal stem cells, can be efficiently isolated from bone marrow and/or aspirates. BMSCs can be separated from the rest of the haematopoetic cell fraction by adherence to plastic, followed by negative selection for CD34+ haematopoetic stem cells using magnetic or fluorescent cell sorting. Bone marrow stromal cells promise a minimally invasive, autologous source of cells for transplantation and have been used successfully in cell-based transplant strategies for numerous unrelated diseases.

In terms of SCI, there is conflicting evidence about whether BMSCs can improve post-injury recovery. There is general agreement in the literature that whatever modest benefits may be conveyed will be a result of indirect environmental modification rather than direct translineage conversion of BMSCs to oligodendrocytes or neurons. Although neurogenesis is possible *in vitro* (Rismanchi et al., 2003), there is debate over whether this occurs to any meaningful extent in adult tissue *in vivo* (Castro et al., 2002; Mezey et al., 2003; Vallières and Sawchenko, 2003). BMSC transplantation provides tissue sparing in penumbral regions, and cells are thought to be neuroprotective and reduce apoptosis, inflammation and demyelination (Akiyama et al., 2002; Ankeny et al., 2004; Sasaki et al., 2009). BMSCs can also mobilise endogenous NSPCs (Mahmood et al., 2004a; Bonilla et al., 2009) as well as provide physical scaffolding for elongating axons (Ankeny et al., 2004; Hofstetter et al., 2002). There is evidence that BMSCs are associated with locomotor restoration (measured by BBB open field test), as well as increases in trophic factors that can lead to enhanced angiogenesis and normalization of blood flow (Mahmood et al., 2004b; Hu et al., 2005; Parr et al., 2007). However, these observations are fraught with inconsistency: in a systematic review, Tetzlaff et al. (2010) observed that of six non-hemisection SCI models that used human BMSCs, three reported benefits, and three found no difference after transplant (Kim et al., 2006; Himes et al., 2006; Cízková et al., 2006; Lee et al., 2007; Deng et al., 2008; Sheth et al., 2008). These six studies showed no universal consistency in terms of donor age/sex, cell passaging/culture conditions, the use of cryopreserved or fresh cells and separation via plastic or multiple sources. In addition, a further study by Neuhuber et al. (2005) showed that experimental outcome varied based upon BMSC donor. As the mechanism by which BMSCs function remains elusive, and considering the inconsistency associated with cell-sourcing and selection conditions currently employed, further study must be done to isolate and characterise more homogeneous cell BMSC populations to glean reliable, replicable results.

Schwann cells (SCs)

Although SCs are not multipotent progenitors, they have plastic characteristics that facilitate regeneration and make them, historically, one of the most widely transplanted neural cells in SCI. SCs naturally populate the growth-permissive peripheral nervous system (PNS) and their grafts can act as a bridge, supporting axonal outgrowth following neural injury. Mature myelinating or non-myelinating SCs develop from neural crest-derived immature SCs; however, during the injury response, SCs revert from a mature phenotype back into immature SCs via c-Jun mediated pathways (Parkinson et al., 2008). Although they can act as both trophic and physical substrates to facilitate axonal growth, the environment they create is often so permissive that axons are reluctant to leave SC grafts, limiting clinical applicability (Raisman, 1997; Campbell et al., 2005). In addition, some axons, such as those of the corticospinal tract (CST), remain unaffected by SC grafts (Tetzlaff et al., 2010). Consequently, combinatorial strategies have been developed which unite the intrinsic axon growth-promoting properties of SCs with bioengineering products or adhesion molecules to help aid in functional axonal regeneration through the lesion site and to enhance plasticity and recovery (Tom and Houle, 2008; Houle et al., 2006; Lavdas et al., 2010; Fouad et al., 2005). Also, to avoid potential harvest-associated hazards, alternative SC sources have recently been explored, including skin (Biernaskie et al., 2007; McKenzie et al., 2006) and bone marrow (Kamada et al., 2005; Wakao et al., 2010; Park et al., 2010).

There is also some evidence suggesting that, following spinal cord injury, the CNS is capable of generating Schwann or Schwann-like cells which extrude periaxin + myelin, typical of PNS but not of CNS myelination (Gillespie et al., 1994; Blakemore and Franklin, 2008). This phenomenon occurs not only after NSPC transplantation into the injured CNS but also with endogenous precursors following demyelination. Fate mapping analysis shows that after induced demyelination the majority of Schwann cell-like cells naturally present at the lesion site originate from endogenous CNS precursors, although some PNS-derived Schwann cells can migrate from the periphery into the lesion through a disrupted glia limitans (Zawadzka et al., 2010).

Olfactory ensheathing cells (OECs)

OECs possess certain properties, which resemble PNS SCs and CNS astroglia. Derived from the olfactory bulb or, less invasively, through the lamina propria of the olfactory mucosa, they exhibit lifelong proliferative capacity and normally act as intermediary glial cells, mediating the transition between axons in the PNS olfactory mucosa and their synapses in the CNS olfactory bulb (Doucette, 1991). Lineage tracing evidence suggests that OECs originate from the neural crest, which raises the possibility of future skin-derived autologous expansion and transplantation strategies (Barraud et al., 2010). Like SCs, OECs promote axonal regeneration through the lesion site and can facilitate axon re-entry at graft–host border zones. Differences in cell origin and *in vitro* passaging have been linked to variable OEC efficacy (Au et al., 2007; Richter et al., 2005). Use of OECs for SCI has been thoroughly studied; however, human trials have shown mixed results (Lima et al., 2006, 2010; Mackay-Sim et al., 2008; Chhabra et al., 2009). These reports are in line with animal studies that showed inconsistent OEC regenerative capacity (within olfactory mucosal grafts) in independently replicated experiments (Steward et al., 2006). Alternative means of cell transplant have thus been explored.

Neural stem/progenitor cells (NSPCs)

There is a promising sub-population of stem cells naturally present in adult neural tissue. Multipotent brain adult (a)NSPCs reside primarily in the periventricular sub-ependymal layer and the subgranular zone of the dentate gyrus. In the spinal cord, multipotent

progenitor pools can be found in the ependymal regions lining the central canal (Hawryluk and Fehlings, 2008). Astrocyte and oligodendrocyte progenitors are distributed throughout the parenchyma of the spinal cord. Fate-mapping analysis suggests that in the uninjured cord, ependymal, astrocytic and oligodendroglial progenitors maintain homeostatic precursor cell numbers with oligodendroglial progenitors differentiating at a 2-fold increase every 4 months (Barnabé-Heider et al., 2010). It was previously thought that the mammalian CNS lacked endogenous plasticity; however, mounting evidence suggests that progenitors—particularly multipotent ependymal cells—are capable of expansion following injury (Meletis et al., 2008; Hawryluk and Fehlings, 2008; Zawadzka et al., 2010; Barnabé-Heider et al., 2010). In the spinal cord, these ciliated ependymal progenitors are capable of honing in on the lesion site and producing both astrocytic-like and oligodendroglial lineage cells following SCI, suggesting that there exists more CNS-intrinsic regenerative potential than was originally postulated.

Both brain and cord-derived aNSPCs can be propagated *in vitro* (Weiss et al., 1996; Shihabuddin et al., 1997) and promote functional recovery when transplanted into the injured or dysmyelinated spinal cord (Eftekharpour et al., 2007; Moreno-Manzano et al., 2009). There is evidence that, upon receiving appropriate trophic cues from the *in vivo* CNS environment, transplanted aNSPCs—which possess the ability to generate neurons *in vitro*—differentiate almost exclusively into glia, with minimal neuronal differentiation observed (Nakamura et al., 2005; Pfeifer et al., 2006; Karimi-Abdolrezaee et al., 2006, 2010; Mothe and Tator, 2008). Thus far, strategies to attract endogenous NSPCs to the site of injury have been insufficient to stimulate functional remyelination (Mitchell et al., 2004), even with supplementary pharmacological stimulation (Barnabé-Heider and Frisén, 2008; Bambakidis et al., 2003; Kojima and Tator, 2002). Although aNSPCs are the ideal candidate for cell transplantation studies—their utilisation begets functional improvement, shows low rates of tumourigenesis and provides the opportunity for autologous transplantation—the relative scarcity of NSPCs in the mammalian CNS, combined with risks related to their harvest, limit the clinical translation of aNSPC-derived cell therapy. Therefore, methods of robust NSPC generation with patient specificity and without invasive techniques were developed using induced pluripotent cells (vide infra).

Embryonic stem cells (ESCs)

Isolated from the inner cell mass of the early blastocyst, ESCs possess the ability to differentiate into lineages derived from all three primary germ layers—ectoderm, mesoderm and endoderm. First characterised in murine (Evans and Kaufman, 1981; Martin, 1981) and later in non-human primate (Thomson and Marshall, 1998) and human (Thomson et al., 1998) models, ESCs are particularly versatile. ESCs can be effectively cultured, undergo multiple freeze/thaw cycles, and maintain long-term differentiation potential and normal karyotype even following several generations of passaging and expansion (Ko et al., 2007; Richards et al., 2002). The most important aspect of ESCs in cell-based therapy is that they have been shown to be capable of deriving cells that are nearly indistinguishable from neural progenitors and mature cell types and have been used to efficiently repair SCI (reviewed by Tetzlaff et al., 2010; Salewski et al., 2010). While ESCs are extensively characterised and transplantation may seem suitable, there are associated caveats that must be addressed before successful clinical translation. As with any allogenic transplantation, patient immunosupression will be necessary, and there is evidence that immunosuppressive regimes, in conjunction with ESC transplant, may be insufficient to thwart a continued immune response (Drukker et al., 2006; Grinnemo et al., 2006; Preynat-Seauve et al., 2009). A formative characteristic of ESCs is the ability to form teratomas upon transplantation; subsequently, there is a proscriptive risk of tumourigenicity should any pluripotent cells remain in a graft of ESC-derived neural progenitors. Indeed, when transplanted into the spinal cord, partially differentiated ESC cultures caused tumours in rodent models (Matsuda et al., 2009). In addition to the genetic and immunogenic concerns, ESCs have also generated an ethical debate surrounding the use of human embryos.

Induced pluripotent stem cells (iPSCs)

More recently, the reversion of somatic cells into pluripotent states has become possible. Upregulation of 4 "Yamanaka factors"—octamer 3/4 (OCT4), SRY box-containing gene 2 (SOX2), tumour suppressor Kruppel-like factor 4 (KLF4) and proto-oncogene C-MYC (or non-tumourigenic substitute L-MYC)—allows somatic cells from mice and humans to be reprogrammed back into pluripotent cells that recapitulate many properties of ESCs, such as tri-lineage differentiation and generation of viable chimaeras (Nakagawa et al., 2008; Takahashi and Yamanaka, 2006)(Takahashi and Yamanaka, 2006; Nakagawa et al., 2008, 2010). These cells are patient-specific and circumvent popular ethical issues associated with the harvest of ESCs (Salewski et al., 2010). Induction to pluripotency can also be done without the need for potentially hazardous viral vectors through the use of piggyBac transposon system (Woltjen et al., 2009; Kaji et al., 2009), non-integrating excisable virus (Soldner et al., 2009; Sommer et al., 2009), drug selectable targeting (Yu et al., 2009), chemicals and small molecules (Huangfu et al., 2008) and protein iPSCs (Cho et al., 2010; Zhou et al., 2009; Kim et al., 2009). Unfortunately, these reprogramming methods are inefficient, and pluripotent cells will likely not be allowed in initial clinical trials due to concerns surrounding long-term tumourigenicity.

To make treatment-ready cell populations, pluripotent stem cells (derived from both ESC and iPSC populations) must first be differentiated into a dedicated cell lineage. Once performed with multi-stage processes using high dose retinoic acid and growth factors (Bain et al., 1995), this is now accomplished by inhibition of bone morphogenetic proteins or removal of external growth cues, the so-called "default pathway" for pluripotent cells (Smukler et al., 2006; Chambers et al., 2009). This protocol produces neurospheres comprised of multipotent NSPCs ($\leq$1%) and fate-restricted precursors that generate neurons, astroglia, and oligodendroglia (Liu et al., 2000; Morshead et al., 2002; Wada et al., 2009). These primitive neural stem cells also pose a risk of tumourigenicity (Nakagawa et al., 2008; Wernig et al., 2008); therefore, transplanted populations derived from pluripotent cells must be purified and devoid of non-specialised or unrestricted populations.

Powerful reprogramming technologies have been developed that can generate iPSCs with transiently applied synthetic mRNA at high efficiencies, removing the need for viral or genomic manipulation and allowing for direct clinical translation (Warren et al., 2010). This technology can rapidly differentiate neural cells from pluripotent cells, or even programme neural cells directly from skin or peripheral blood cells (Vierbuchen et al., 2010; Yamanaka, 2010). For the first time, clinically translatable cell manipulation is available that possesses the potential to produce abundant, autologous and safe cells for transplantation.

Plasticity in SCI: a key mechanism of inducing repair and recovery

Stem and associated cells are particularly useful tools for regenerative medicine. Transplanted cells can exert plastic changes by remyelinating denuded axons, increasing chemotaxis, promoting neurite outgrowth and by reducing cell death and axonal dieback. Potential therapeutic cell types (vide supra) induce these plastic changes through physical support and scaffolding for axons and by secreting trophic factors for neuroprotection and enhanced cellular injury response.

Structural support and myelination

There is evidence that pluripotent-derived stem cells can differentiate into both neurons and oligodendrocytes *in vitro* that can be used in tissue replacement strategies for CNS repair—for review, see Ruff and Fehlings (2010). It should be noted that, although neuronal cell replacement is a feasible option for other conditions (e.g. secretory cell replacement), long descending motor tracts that comingle with pain fibres limit the clinical application of stem cell-derived neuronal replacement strategies in SCI. Instead, stem cell replacement strategies most often focus on replacing the glial environment. Schwann cells, NSPCs and OECs have inherent glial and myelinating properties. Schwann cells can ensheathe motor and sensory neurons in 3-D and 2-D *in vitro* culture systems, and although axons associate with but are not myelinated by OECs in situ, *in vitro* assays indicate that both adult and juvenile olfactory bulb-derived OECs are capable of anatomical remyelination of DRGs (Gingras et al., 2008; Babiarz et al., 2010). Schwann-like cells derived from BMSCs are also able to express (at both RNA and protein levels) myelin protein zero, peripheral myelin protein 22 and myelin basic protein (MBP) in DRG co-cultures (Mantovani et al., 2010). Several studies also show that pluripotent cells can derive OPCs, which are capable of extruding MBP and compactable myelin in organotypic co-culture and traditional *in vivo* settings (Liu et al., 2000; Kang et al., 2007; Izrael et al., 2007; Chen et al., 2010; Cui et al., 2010; Sundberg et al., 2010). All of these cells, including BMSCs, are capable of filling lesion cavities and providing structural integrity to the injury site, preventing further damage.

Neurotrophic factor mediation of plasticity

Perhaps the most important role of stem and associated cell transplantation for SCI lies not with physical support, but in the considerable capacity of transplanted stem cells to become trophic mediators in the neuronal regenerative response. Stem cells secrete key intermediates that can enhance neuronal survival, axonal sparing, plasticity and regeneration (Teng et al., 2002, 2006). Traditionally, studies investigating axonogenesis have focused on production of the 'classic' neurotrophin family—nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3), and neurotrophin-4/5 (NT-4/5). It is important to note that some evidence suggests that NGF may also induce hyperalgesia by mediating plasticity of nociceptive circuitry (Ji et al., 2002; Hefti et al., 2006; Ruiz and Baños, 2009). In addition, cytokine growth factors and transforming factor-β (TGF-β) family members, including glial cell-line derived neurotrophic factor (GDNF), can also support axonal outgrowth in SCI models, each playing a distinct but overlapping role (Moalem et al., 2000; Jones et al., 2001; Glazova et al., 2009; Peng et al., 2003). Fibroblast growth factor (FGF) isoforms have also been linked in to survival and neurite outgrowth in certain neuronal subtypes (Pataky et al., 2000). Ciliary neurotrophic factor (CNTF), secreted by glial cells and some BMSCs, can enhance neurite outgrowth when applied topically (Tebar et al., 2008) and promote oligodendrocyte differentiation and OPC/neuronal survival (Zochodne and Cheng, 2000; Sleeman et al., 2000; Tebar et al., 2008; Jiang et al., 2010; Cao et al., 2010). Neurotrophic modulation is purportedly the primary mechanism of BMSCs, which are known to secrete BDNF, NGF, VEGF, TGF-β, IGF1, BNP and SCF1 (but not NT-3 or NT-4)—potent chemotropins involved in axonal outgrowth, neuronal and glial survival and angiogenesis (Mahmood et al., 2004b; Hu et al., 2005; Crigler et al., 2006; Parr et al., 2007). Bone marrow stromal cells induced to become Schwann-like cells showed additional upregulation of hepatocyte growth factor (HGF), VEGF, BDNF and NGF, promoting neuritogenesis and neuron preservation in co-cultures and *ex vivo* preparations (Park et al., 2010; Mahay et al., 2008). *In vitro* studies examining OEC/neuronal co-cultures also display upregulation of neurotrophins midkine, HGF, activin A, TGF-β, BDNF and the chemokine stromal cell-derived factor-1α (SDF-1α), as well as its receptor CXCR4, further increasing axonal elongation and cell survival (Zhang et al., 2006; Shyu et al., 2008).

As with other biological instruments, stem cells possess unique characteristics that act in a context-specific manner as boon and burden, with myelination capacity, chemotrophic potential and endogenous presence varying between cells. Therefore, *in vitro* mechanisms of cellular actions must be evaluated by *in vivo* modelling systems.

Promoting recovery in animal models

Stem and progenitor cells demonstrate mechanism of action in host tissue, suggesting potential for regenerative plasticity in human SCI (Fig. 2). However, while identifying individual cause–effect relations, *in vitro* investigation cannot measure gross effect on tissue. This must be explored using *in vivo* paradigms. The promotion of recovery can be perceived as any factor that increases the ability for beneficial endogenous reorganisation within the region of the lesion and indeed throughout the length of the spinal cord (Grasso et al., 2004).

Anatomic plasticity

Several cell types greatly increase axonal regeneration and fibre density in the injured spinal cord. Schwann cell and OEC grafts exhibit extensive axonal growth and elongation (Xu et al., 1995; Ramón-Cueto et al., 1998) with axonal sprouting (Guest et al., 1997). Although they provide an efficient scaffold, axons are reticent to re-enter the CNS (Takami et al., 2002; Pearse et al., 2007). However, SCs can induce growth into lesion cavities if injected directly as a cell suspension (Biernaskie et al., 2007). Similarly, OECs induce axonal regeneration, sprouting and PNS interface crossing (Ramón-Cueto et al., 1998; López-Vales et al., 2006). However, neither cell type is able to significantly affect corticospinal fibre regeneration, or crossing of lesion sites, especially in the chronic stage (Deumens et al., 2006; López-Vales et al., 2007; Guest et al., 2008). In some cases, increased axonal plasticity does not translate to functional recovery of locomotion in studies of SCs or chronic studies of OECs (Pearse et al., 2007). Transplanted NSPCs demonstrate moderate increases in axonal sprouting and regeneration, including the CST (Pfeifer et al., 2004; Hofstetter et al., 2005; Karimi-Abdolrezaee et al., 2010). Injection of BMSCs may increase axon density in the lesion site (Lu et al., 2007); however, this is likely due to tissue sparing as transplanted cells do not integrate well with host tissue.

Lesion modification

Environmental modification and tissue sparing are potentially more efficacious approaches to increase plastic repair. Gliosis and astrocyte reactivity has been shown to be reduced with transplantation of OECs in acute SCI (Lakatos et al., 2003; López-Vales et al., 2006) and of BMSCs in acute and chronic SCI (Lu et al., 2007) but may be increased by SC transplants. Tissue sparing and increases in grey and white matter have been demonstrated in nearly all cell transplantation approaches, with increases in white matter most pronounced with NSPCs and glial-restricted progenitors (Mitsui et al., 2005; Karimi-Abdolrezaee et al., 2010). Neural precursor cells can efficiently remyelinate host axons with organised, compact myelin (Keirstead et al., 2005; Eftekharpour et al., 2007). Oligodendrocyte precursors can remyelinate in chronic stage lesions, but only if the glial scar is degraded (Keirstead et al., 2005; Karimi-Abdolrezaee et al., 2010). Schwann cells and OECs wrap injured axons in peripheral myelin (Pinzon et al., 2001; Takami et al., 2002) but require trophic adjuvants to functionally remyelinate host tissue.

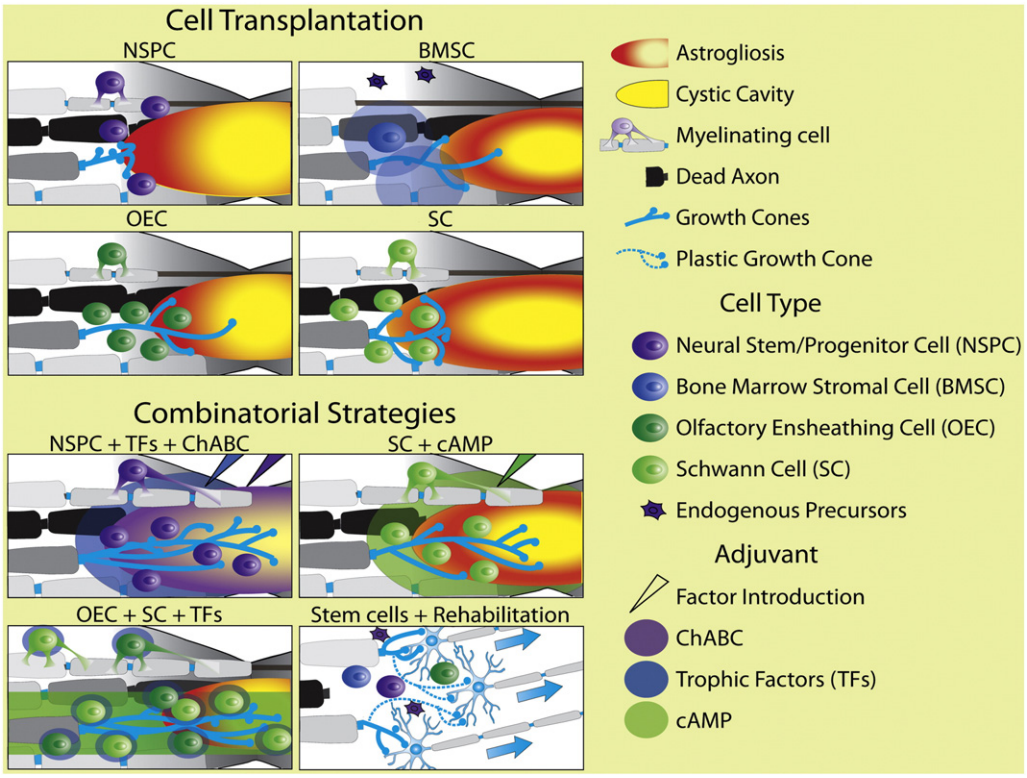

Fig. 2. Cell transplantation for SCI. (Top) Neural stem/progenitor cell (NSPC) transplantation can functionally remyelinate the injured cord, whilst elongating axons are hindered by the glial scar. Bone marrow stromal cell (BMSC) transplantation does not remyelinate axons but can enhance trophic support to increase axonal outgrowth and decreasing lesion cavity size and axonal dieback. Olfactory ensheathing cells (OECs), while displaying poor lesion-site survival, are able to myelinate axons, decrease lesion cavity size, secrete low levels of trophic factors, and integrate into the glial scar to facilitate limited axonal outgrowth. Axons grow well into Schwann cell (SC) grafts and are able to bridge the lesion site but are reluctant to leave grafts. SCs can myelinate damaged axons and secrete trophic intermediates, although there is evidence to suggest that SCs increase astrogliosis. (Bottom) In combination and with appropriate scar degradation and trophic support, NSPCs can integrate into the lesion, differentiate into oligodendrocytes, promote robust myelination and fibre extension into the lesion. This enhances behavioural outcomes. In multiple cell combination, OECs and SCs modified to secrete trophic factors facilitated remyelination and outgrowth into the lesion site, as well as decreased cavity size and tissue sparing. With accompanying upregulation of cAMP via systemic administration, SCs showed enhanced remyelination as well as robust axonal outgrowth. Rehabilitation has been used in conjunction with several stem cell types, including BMSCs, NSPCs and OECs, to enhance local sprouting and promote functional plasticity in descending motor tracts and sublesional locomotor systems.

Physiologic recovery

The most important outcome measures are electrophysiology and behavioural function: these will indicate the ultimate efficacy of a putative treatment. Electrophysiological analysis is available for each cell type. Following transplantation of NSPCs and glial-restricted progenitors, electrophysiology of the cord consistently and significantly increased in motor evoked potential (MEP), somatosensory evoked potential (SSEP), cortical MEP and cortical SSEP (Bambakidis and Miller, 2004; Pan et al., 2008; Meng et al., 2008). Every study that shows physiologic improvement also demonstrates significant improvements in BBB locomotor scores and paw kinematics. Despite being the longest and most studied, SC transplantation has few electrophysiological analyses. Nonetheless, SC transplantation does increase conductance of the spinal cord (Pinzon et al., 2001). Similarly, BMSCs have been shown to return electrophysiology and motor function in higher animals, such as the pig and rhesus monkey (Deng et al., 2006; Zurita et al., 2008). Recently, Pedram et al. (2010) reported that RA-based differentiation of BMSCs improved BBB scores in acute SCI. There is emerging evidence that BMSCs are also effective when homing to the injured spinal cord following administration via intrathecal or intravenous routes, resulting in recovery including improved locomotor scores and increased tissue sparing (Syková and Jendelová, 2005; Paul et al., 2009; Osaka et al., 2010; Cizkova et al., 2010); however, additional studies are needed to confirm these findings. Electrophysiological analysis following OEC transplantation has been often performed, revealing improved conductance and lower latency across the lesion (Imaizumi et al., 2000), via transcranial MEP (Deng et al., 2008), SSEP and CMEP (Toft et al., 2007). These returns in physiology are correlated with increased BBB scores and often in the absence of axonal regeneration (López-Vales et al., 2007; Toft et al., 2007).

Potentially harmful effects of promoting plasticity

There is reason to believe that neuropathic pain and/or spasticity could result from poorly conceived transplantation approaches. Evidence of pain-like behaviour has been observed with use of multipotent NSPCs in rodent SCI (Hofstetter et al., 2005; Macias et al., 2006). Decreased thresholds required to elicit a pain-like response to mechanical and thermal stimulus (allodynia) were seen in forepaws of injured rats following NSPC transplant, coinciding with upregulation of GAP43/CGRP expression and increased fibre density in dorsal horns. Hofstetter et al. (2005) determined that directing NSPCs to oligodendroglial and neuronal fates functioned not only to decrease undesired allodynic behaviour but also to further improve locomotion and ascending cortical stimulation. There have also been reports of autotomy and neuropathic pain following transplantation of OECs from the lamina propria of the olfactory mucosa (Richter et al., 2005). Tonic spasticity was also seen in the hindlimbs of OEC transplanted rats during gridwalk (Guest et al., 2008). Indeed, a human pilot study using grafts of olfactory mucosa (containing OECs) in a chronic injury model reported treatable pain in 2 of 7 patients (Lima et al., 2006). While reports of harmful effects from cell transplantation are rare, careful attention must be paid to recognize potentially negative

consequences posed by cell-based transplantation and to modify strategies to preclude adverse effects.

Clinical translation

Behavioural recovery has been shown in contusive thoracic models with consistent benefits from NSPCs, SCs and BMSCs, with varied reports and transient recovery in OECs (Guest et al., 2008). This is intriguing because the mechanism of BMSC efficacy is still obscure, and myelination of NSPCs was once considered controversial. Efficacy of promoting functional recovery has been widely studied in thoracic rodent models, along with a smaller number of pig, dog and primate models. To enhance the likelihood of successful clinical translation of experimental strategies, future preclinical combinatorial studies should increasingly involve cervical lesions and chronic stages of injury. The results previously obtained should ideally be confirmed, at least in part, in large animal models due to lesion size confounders. There is a paucity of such studies, with independent evidence for chronic injury and large animal models available only for NSPCs and BMSCs. Recently, a sacrocaudal SCI model for NSPC transplantation in cloned Yucatan minipigs has been developed and might pave the way for future combinatorial strategies (Lim et al., 2010). While there are numerous studies reporting negative or inconsistent results, the majority of studies have reported positive effect on tissue plasticity and behavioural recovery—especially when therapeutic agents are combined. Furthermore, given the complexity and size of lesions, it is likely that optimal clinical therapeutic strategies in humans will involve combinatorial approaches.

Combinatorial strategies

Acknowledgment of incremental recovery observed following simple transplant of cells led, over the previous decade, to the application of combination strategies (Fig. 2). To test for summation of effect—and, indeed, synergisms—that could boost clinical efficacy, cell transplantation has been applied with combinatorial additions of growth factor(s) and other cell types, scar degradation, electrical stimulation, and rehabilitation.

Neurotrophin administration

The most widely studied combination strategy is viral-transduction and infusion of growth factors. BDNF and D15A (that has BDNF and NT-3 activity) increase regeneration and reduced dieback of brain–spinal axons and confer locomotor recovery when transduced into SCs (Menei et al., 1998; Hurtado et al., 2006). Axonal plasticity and behavioural recovery was not always conferred by BDNF or NT-3 transduction in BMSCs (Lu et al., 2004; Koda et al., 2007). Infusion and over-expression of FGF-2/EGF or NT-3/BDNF, in conjunction with NSPCs or fate-restricted progenitors, respectively, have been shown to increase oligodendroglial differentiation and myelination, up to 4-fold increased axonal density, up to 9 mm of axonal growth, and summative behavioural benefit in BBB, gridwalk, and electrophysiological outcomes (Lu et al., 2003; Cao et al., 2005; Guo et al., 2007; Karimi-Abdolrezaee et al., 2010; Bonner et al., 2010). Similar results of differentiation, neuroplasticity and behavioural recovery are seen in NSPCs with G-CSF, BDNF and CNTF in a dose-dependent manner (Pan et al., 2008; Cao et al., 2010). Few combinations of growth factor with SCs or NSPCs have returned negative results. Growth factors should not be added blindly, as Bretzner et al. (2008) demonstrated that addition of BDNF to OEC transplantation increased lesion cavitation, with worsened forelimb reaching and coordinated walking.

Cell coupling

Combining two progenitor cell types has also shown additive benefit to plasticity and functional recovery. Several groups have pursued the combination of SCs with OECs. This has the result of increased axonal entrance and egress from SC grafts, and myelination of fibres including 5HT+ axons (Pearse et al., 2004a; Fouad et al., 2005). Greater improvements in locomotion, with respect to SC alone, were also conferred (Pearse et al., 2007). Finally, combining SCs with NSPCs resulted in increased effect on electrophysiology and BBB scores (Guo et al., 2007). A similar approach to increasing the regenerative capacity of host tissue was pursued by increasing cAMP levels in the injured cord. Elevating cAMP levels has been shown to allow axons to regenerate beyond inhibitory cues in the spinal cord (Cai et al., 2001) presumably by an increased intrinsic growth response. Local and systemic elevation using db-cAMP or Rolipram has been shown to promote axonal growth into and beyond SC, OEC and MSC grafts, along with reduced astrocytosis and improvement in locomotion (Pearse et al., 2004b; Bretzner et al., 2010). However, beneficial results are not seen when cAMP is upregulated in the absence of co-administered neurotrophins (Lu et al., 2004)or cells (Pearse et al., 2004b; Bretzner et al., 2010) and has been shown to possibly decrease survival of grafts (Nout et al., 2010).

Targeting the glial scar

Degradation of the glial scar is a particularly promising arm of combination strategies. Comprised primarily of reactive astrocytes, the glial scar contains extracellular matrix molecules called chondroitin sulphate proteoglycans (CSPGs), which contain a moiety that is inhibitory to axon growth (Bradbury and Carter, 2010). While axons and myelinating cells are readily able to grow and migrate lesion-relative distance (Kerschensteiner et al., 2005; Ikegami et al., 2005; Karimi-Abdolrezaee et al., 2010), it is the inhibitory glial scar that impedes plastic regeneration. The bacterial enzyme Chondroitinase ABC (ChABC) cleaves CSPG moieties and degrades the gliotic scar and has been applied alone, in combination with NSPCs, and SCs with or without OECs. Application of ChABC in conjunction with SC + OEC transplantation resulted in significant improvements in axonal plasticity, axon growth within grafts, peripheral myelination and locomotion (Fouad et al., 2005; Vavrek et al., 2007). In conjunction with NSPCs, migration of transplanted cells is increased by ChABC administration (Ikegami et al., 2005). Our lab recently demonstrated that a combination of ChABC, NSPCs and growth factor infusion resulted in dramatic increases in transplant migration, oligodendroglial differentiation, serotonergic axon density, axonal plasticity and functional recovery without allodynia (Karimi-Abdolrezaee et al., 2010). With additional reports of synergism with careful rehabilitation (Garcia-Alias et al., 2009), scar degradation will likely be an integral part of combinatorial strategies. Vaccination with myelin-associated proteins has also been effective in collaboration with NSPCs (Ziv et al., 2006; Xu et al., 2010). Additional strategies have been developed in conjunction with progenitor cell transplantation, including increased adhesion via L1-transduction, swimming training, and electric stimulation (Chen et al., 2008; Carvalho et al., 2008; Yan et al., 2009; Lavdas et al., 2010). These new approaches require confirmation by additional research groups and in other SCI model paradigms.

While the propensity for success of combinatorial approaches is encouraging, promising outcomes must be reliably reproduced. With the great disparity of cell sources, delivery methods and injury models used, more robust evaluation of therapeutic potential of these combinations will distinguish true benefits from anomalies. Furthermore, conducting clinical trials of combination strategies is a daunting consideration.

Fortunately, a clinical trial of human OPCs is in now in progress (Geron Corp, Menlo Park CA) and should pave the way for future cell-based trials. Briefly, Geron is using highly purified human ESC-derived OPCs for a phase I safety/feasibility study in 10 patients with complete (ASIA-A) thoracic spinal cord injuries at 7–14 days post-injury (Alper, 2009). It is very likely that additional phases of the clinical trial will be required to demonstrate the potential efficacy of pluripotent cell-derived transplants; however, this is a pivotal study representing translation of animal model data of cell-based SCI therapy to human clinical use.

Conclusions

Stem cells facilitate axonal outgrowth by secretion of trophic intermediates and enhance neurite outgrowth, axonal elongation and fibre density across the lesion cavity. Trophic modification can also activate resident or transplanted progenitor cells, reduce the inflammatory response and lessen cystic cavity formation. Addition of exogenous growth-associated factors can act synergistically to mediate local plasticity and functional recovery. Damaged axons may regenerate through lesions if intrinsic growth mechanisms are bolstered, and extrinsic barriers are diminished. Therefore, many combinatorial strategies employed ChABC to degrade the glial scar or OECs to facilitate lesion entry (Andrews and Stelzner, 2007), providing robust axonal elongation across the lesion. Stem cells also promote remyelination via oligodendroglial cell replacement, leading to neuronal and gross tissue sparing. Remyelination of key fibre tracts influences motor and sensory systems can initiate new pathways with undamaged tracts that bypass the lesion, further preserving sublesion function. Increased connectivity to and activation of unmasked circuits can reorganise pre-existing central pattern generators (Grasso et al., 2004). Similarly, several investigations show enhanced functional recovery without accompanying axonal growth beyond the lesion (Takami et al., 2002; Yamamoto et al., 2009; Karimi-Abdolrezaee et al., 2010). Rehabilitative approaches based on the presence of pre-existing neural networks can further enhance functional recovery, as exercise increases progenitor activation in the injured CNS and enhanced plasticity of task-specific circuits (Garcia-Alias et al., 2009; Foret et al., 2010).

Although component properties of stem cells can enhance recovery following SCI, no single cell type, when transplanted, seems sufficient to support a robust regenerative response. Patient-specific approaches, such as using autologous SCs, OECs, BMSCs and iPSC technologies, provide a highly translational and clinically relevant source of cells for transplant. Further reproducible studies using large animal and primate models can establish safety and feasibility of stem cell transplantation for human SCI. Considering high patient demand and precedents set by current clinical trials of stem cell therapy, if suitable preclinical data can be gathered, combinatorial stem cell therapy for SCI could provide a means by which functional recovery could be restored. Transparent communication and cooperation between clinicians, researchers, policymakers and the public can move potential strategies one step closer to preventing damage and treating SCI.

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