

Potential of olfactory ensheathing cells for cell-based therapy in spinal cord injury

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Abstract—Contusive spinal cord injury (SCI) results in a complex lesion that includes cellular and axonal loss, microglia and macrophage activation, and demyelination. These changes result in permanent neurological deficits in people with SCI and in high financial costs to society. Unlike the peripheral nervous system (PNS), in which axonal regeneration can occur, axonal regeneration in the central nervous system (CNS) is extremely limited. This limited regeneration is thought to result from a lack of a permissive environment and from active inhibitory molecules that are present in the CNS but minimal in the PNS. Currently, cell transplantation approaches are among several experimental strategies being investigated for the treatment of SCI. In the olfactory system, a specialized glial cell called the olfactory ensheathing cell (OEC) has been shown to improve functional outcome when transplanted into rodents with SCI, and clinical studies transplanting OECs into patients with SCI are ongoing in China, Portugal, and other sites. Yet, a number of controversial issues related to OEC biology and transplantation must be addressed to understand the rationale and expectations for OEC cell therapy approaches in SCI. This review provides information on these issues for spinal cord medicine clinicians.

Key words: axons, cell-based therapy, cell transplantation, central nervous system, functional recovery, neuroprotection, olfactory ensheathing cell, rehabilitation, remyelination, spinal cord injury.

INTRODUCTION

More than 11,000 traumatic spinal cord injuries (SCIs) are estimated to occur in the United States each year [1]. Unfortunately, aside from good medical management, no generally accepted interventional therapies are available. While neurogenesis has long been thought to occur only during embryogenesis, recent advances in cell biology have identified progenitor cells for neurons and glia in the adult nervous system. These discoveries have given rise to the concept that a cell-based therapy

Abbreviations: BDNF = brain-derived neurotrophic factor, CNS = central nervous system, GFP = green fluorescent protein, GFP-OEC = olfactory ensheathing cell derived from GFP transgenic rats, K_v1 = Shaker-type voltage-gated potassium channel, M1 = primary motor cortex, Na_v = voltage-gated sodium channel, NGF = nerve growth factor, OB = olfactory bulb, OEC = olfactory ensheathing cell, OM = olfactory mucosa, ONL = outer nerve layer, ORN = olfactory receptor neuron, p75NGFR = p75 NGF receptor, PNS = peripheral nervous system, RMS = rostral migratory stream, SCI = spinal cord injury, SVZ = subventricular zone.

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might be developed for patients with SCI (see Reier [2] for an overview). Unlike Parkinson's disease, where the rationale for transplantation therapy is to replace neurons that produce dopamine, a primary objective of spinal cord repair is to regenerate long axonal tracts and remyelinate axons. Thus, while neurons may die at the injury site, neurogenesis of these segmental neurons is considered less important than establishment of new functional axonal links to intact spinal cord circuits below and above the level of injury.

A number of myelinating cells and their precursors have been shown to remyelinate spinal cord axons after transplantation [3]. Neural progenitor cells, which can differentiate into neurons and glia, can be isolated from the adult mammalian dentate gyrus [4], the subventricular zone (SVZ) that lines the lateral ventricles [5–7], and the spinal cord [8] and have been used to remyelinate axons. Importantly, neural progenitor cells isolated from adult human brain can differentiate into neurons and glia [9–11]. Remyelination results when neural progenitors, prepared from biopsy of the SVZ under ultrasound guidance in the nonhuman primate, are transplanted into the demyelinated spinal cord of the same animal [12]. Moreover, neural precursor cells have been prepared from a number of peripheral tissues, such as bone marrow [13], skin, and peripheral blood [14], and active investigation of their potential therapeutic effects in central nervous system (CNS) repair is ongoing. A concern with multipotent "stem cells" is that upon transplantation, they might differentiate into ectopic tissues. For example, bone marrow-derived mesenchymal stem cells can potentially differentiate into cartilage when transplanted into the spinal cord. Clearly, establishing appropriate differentiation methods *in vitro* to prevent undesirable *in vivo* differentiation is essential when a cell type is being considered for clinical transplantation studies.

A unique cell within the olfactory system is a specialized glial cell called the olfactory ensheathing cell (OEC). The OEC has attracted much recent attention and is currently being used in clinical studies in patients with SCI. Within the nasal cavity (olfactory mucosa [OM]), olfactory receptor neurons (ORNs) are replaced by a resident population of stem cells [15]. The axons of the ORNs will regenerate through the olfactory nerve and enter the olfactory bulb (OB) of the CNS, where they will make new synaptic contacts [16–17]. Neurogenesis of the ORNs is unique, as is regeneration of peripheral axons that can successfully navigate entry into the CNS and

establish appropriate functional circuits. Current thinking is that OECs serve as glial guides for the regeneration of ORN axons [18–20]. This guidance property of OECs led to the suggestion that isolation and transplantation of these cells could promote axonal regeneration in the injured spinal cord. The present review discusses the biology of the OEC, OEC transplantation studies in animal models of SCI and demyelination, and ongoing clinical studies in which OECs are being transplanted into patients with SCI.

UNIQUE REGENERATIVE PROPERTIES WITHIN OLFACTORY SYSTEM

Two important neurogenic zones are related to the olfactory system: the neural epithelium in the OM in the periphery and the SVZ in the CNS (**Figure 1**). ORNs are

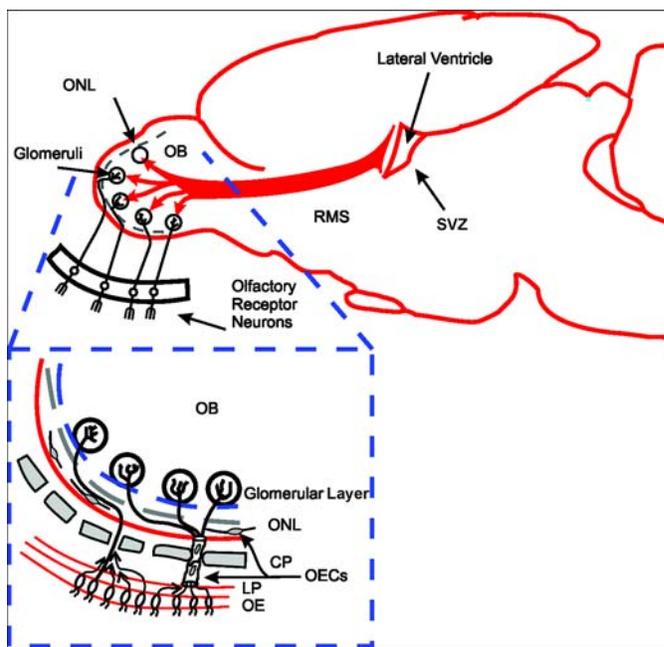


Figure 1.

Basic organization of olfactory system and two important neurogenic zones in adult: subventricular zone (SVZ) and olfactory epithelium (OE). Neural precursor cells in SVZ migrate to olfactory bulb (OB) through rostral migratory stream (RMS) in brain. New olfactory receptor neurons are generated in OE and issue axons that grow into OB to terminate in glomerular layer of OB. These axons are nonmyelinated and grow through glial "tunnels" formed by olfactory ensheathing cells (OECs). OECs bridge periphery and central nervous system and are distributed in outer nerve layer (ONL) of OB. CP = cribriform plate, LP = lamina propria.

continually replaced by a stem cell population in the OM, and neural precursor cells in the SVZ migrate through the rostral migratory stream (RMS) to the OB, where they differentiate into interneurons [21]. The cells that migrate from the SVZ through the RMS are neurogenic cells (“adult stem cells”) that have been harvested for transplantation studies. The reason that neurogenesis is so prominent in the olfactory system is unknown. Given the importance of olfaction for mammalian survival and the potential damage to ORNs from noxious environmental influences, the neurogenic properties of the system may be conserved for survival of the species.

In the peripheral nerve, Schwann cells form basal lamina tubes (bands of Büngner) through which regenerating axons grow. Within the olfactory nerve, the OECs form cellular channels or tunnels through which large numbers of small-caliber nonmyelinated axons distribute through the olfactory nerve into the outer nerve layer (ONL) of the OB and extend into the olfactory glomeruli, where they make synapses (**Figure 1**) [19]. OECs in the ONL are thought to provide a permissive environment that allows entry of ORN axons into the CNS. OECs’ unique property of bridging the peripheral nervous system (PNS) and CNS and providing a channel for peripheral axonal growth into the CNS led to the suggestion that these cells may be therapeutic if transplanted into transected spinal cord tracts [18–19].

ISOLATION OF OLFACTORY ENSHEATHING CELLS FROM OLFACTORY BULB AND OLFACTORY MUCOSA

OECs develop from the olfactory placode and subsequently migrate into the olfactory nerve and OB. This developmental origin contrasts to that of Schwann cells, which arise from the neural crest. From their origin in the OM to their termination in the glomeruli of the OB, the nonmyelinated olfactory nerves are associated with OECs, which surround large numbers of contiguous axons [19,22–24]. The olfactory nerve and the ONL of the OB are enriched in OECs, which have p75 nerve growth-factor receptors (p75NGFRs).

Initial studies have transplanted OECs obtained from OBs into injured spinal cord and demonstrated functional improvement. OECs are present throughout the course of the olfactory nerves and can be harvested at the OM and the OB. Cultures of OECs from the OB [25–26] and the

OM have been described in a number of studies [27]. Lu and colleagues have demonstrated the reparative effects of mucosal-derived cells after intraspinal transplantation [28]. The majority of OECs used in studies on SCI regeneration have been from primary cultures obtained from the rat OB or OM [28–29].

Methods have been developed to purify OECs. OECs have been obtained from embryonic tissue [30], in which the nerve fiber layer is only loosely attached to the marginal zone of the primordial OB [31], thus reducing possible contamination by other OB cell types. Fluorescence-activated cell sorting for O4-positive cells from neonatal tissue has been performed [32]. OEC selection from adult rats has also been performed with the use of immunopanning [33] or magnetic beads against p75NGFR [34]. These methods result in varying degrees of OEC purity and yield. Mixed cultures of OEC and highly purified OEC cultures have been extensively tested as possible therapeutic tools in experimental SCI research [35]. While some studies purified and maintained these cells in culture, other studies used acutely prepared cell suspensions from the OB, which were then transplanted into either SCI models [36] or demyelinated lesion models [37].

TRANSPLANTATION OF OLFACTORY ENSHEATHING CELLS INTO EXPERIMENTAL DEMYELINATED SPINAL CORD LESIONS

In the olfactory nerve, OECs surround large numbers of nonmyelinated axons and normally do not form myelin [38]. However, Franklin et al. first demonstrated that OECs derived from a cell line can form Schwann cell-like myelin, which has the classic signet ring configuration [39]. Subsequently, remyelination by OEC transplants from a variety of species including humans has been reported [37,40–43]. OECs have also been shown to produce myelin when transplanted into the nonhuman primate spinal cord [42].

Green fluorescent protein (GFP)-OECs, or OECs prepared from GFP transgenic rats, were transplanted into a chemically induced demyelinating lesion in the rat dorsal funiculus (**Figure 2**). These cells have a reporter gene to express GFP in their cytoplasm for cell identification [43]. In the sagittal section of the spinal cord shown in **Figure 2(a)**, the transplanted cells (green) are distributing within the demyelinated lesion. Demyelinated fibers from a spinal cord with a chemically induced demyelinated

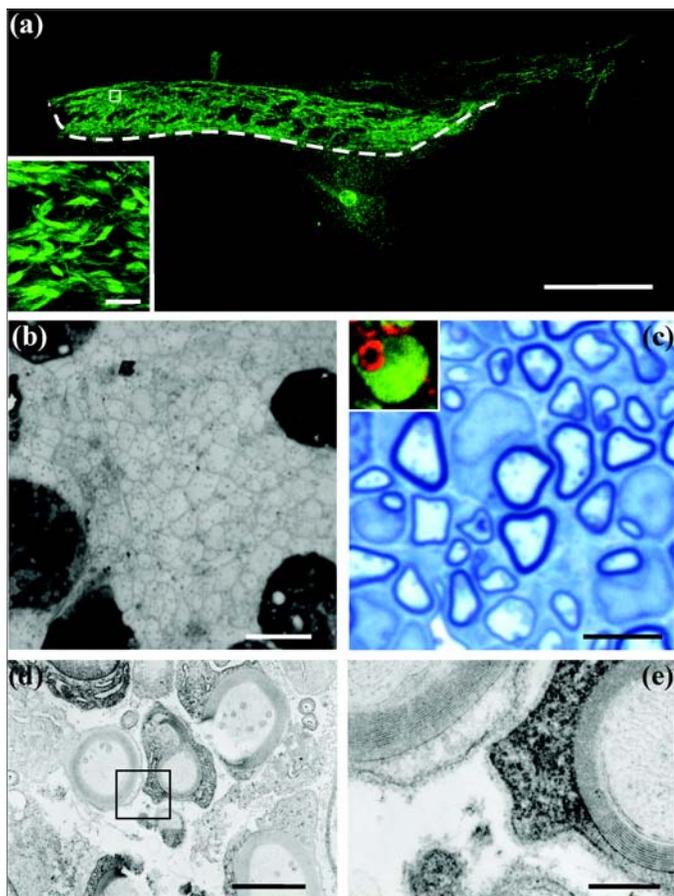


Figure 2.

Histological evidence that transplanted olfactory ensheathing cells (OECs) remyelinate central nervous system axons. **(a)** Sagittal frozen section through chemically demyelinated rat dorsal-column lesion illustrating distribution of transplanted green fluorescent protein (GFP)-expressing rat OECs. Transplanted cells are primarily confined to lesion site. Dashed line demarcates lesion boundary. Inset corresponds to boxed area in **(a)** and shows alignment of OECs with dorsal-column axons. **(b)** Demyelinated axons in spinal cord dorsal funiculus without OEC transplantation. Note large dark macrophages in addition to demyelinated axons. **(c)** Semithin coronal plastic section of spinal cord white matter 3 weeks after OEC transplantation showing peripheral-like myelinated axon profiles within lesion. Inset shows red PO-positive myelin rings associated with green transplanted cell, indicating that transplanted cells produce peripheral-like myelin protein. **(d)–(e)** Immunoelectron micrographs of GFP-OEC transplanted lesions stained with anti-GFP antibody showing that GFP donor cells produce compact myelin. Boxed area in **(d)** is magnified in **(e)**. Note dense reaction product indicating GFP presence and basal lamina associated with myelinating axon on right. Scale bars: **(a)** 1 mm, inset = 20 μm ; **(b)** 10 μm ; **(c)** 10 μm ; **(d)** 2 μm ; **(e)** 0.4 μm . Modified from Sasaki M, Lankford KL, Zemedkun M, Kocsis JD. Identified olfactory ensheathing cells transplanted into the transected dorsal funiculus bridge the lesion and form myelin. *J Neurosci*. 2004;24(39):8485–93. [PMID: 15456822](https://pubmed.ncbi.nlm.nih.gov/15456822/)

lesion without transplantation are shown in **Figure 2(b)**. When OECs were transplanted into the demyelinated lesion, numerous myelinated axons were observed 3 weeks later (**Figure 2(c)**). Immunoelectron microscopy, in which an antibody for GFP is used to identify the transplanted cells on the ultrastructural level (**Figure 2(d)–(e)**), clearly indicates that transplanted OECs can form myelin [44].

However, some investigators have argued that OECs are not the myelinating cells in the just-mentioned studies but that contaminating Schwann cells are responsible for the remyelination [45]. These investigators suggest that OECs, but not Schwann cells, express calponin, a muscle fiber actin-binding protein [46], and that many cells in OEC culture preparations are p75-positive and calponin-negative, thus suggesting that OEC cultures were contaminated by Schwann cells. Franklin et al.'s study in which they used an OEC line and achieved remyelination provides a strong counterargument to the theory that Schwann-cell contamination accounts for remyelination by OECs [39]. A recent study demonstrated that calponin was present in the olfactory fibroblast meningeal cells but not in the adult OECs [47], thus strengthening the argument that OECs can form myelin.

An important aspect of remyelination is that it restores rapid impulse conduction. This restoration is achieved by the high resistance and low capacitance that myelin confers to the axonal membrane and by proper distribution of specific subtypes of sodium and potassium channels [48]. In myelinated axons, voltage-gated sodium channels (Na_vs) are aggregated in high density at nodes of Ranvier, while Shaker-type voltage-gated potassium channels ($\text{K}_v\text{1s}$) are clustered within juxtaparanodal regions and separated from nodal Na_vs by septatelike paranodal junctions [49–51]. Of the seven Na_v isoforms expressed in nervous tissue [52], $\text{Na}_v\text{1.6}$ is the predominant Na_v at mature nodes of Ranvier in both the PNS and CNS [53–54], following a transition from $\text{Na}_v\text{1.2}$, which is present along premyelinated axons and at immature nodes [53,55–57]. The clustering of Na_vs [58–59] and the transition from $\text{Na}_v\text{1.2}$ to $\text{Na}_v\text{1.6}$ [53,57] at nodes has been shown to critically depend on the axon interacting with myelinating glial cells, with both oligodendrocytes [60] and Schwann cells [61]. Thus, determining whether axons remyelinated by OECs respond by establishing appropriate mature nodal ion channel organization is critical.

We examined spinal cord dorsal funicular axons that were remyelinated by transplanted GFP-OECs to facilitate their identification. We demonstrated that GFP-OECs form compact myelin and establish ultrastructurally intact

nodes of Ranvier [62]. $Na_v1.6$ is the predominant Na_v at these remyelinated nodes (**Figure 3(a)–(h)**), and $K_v1.2$ is aggregated in remyelinated juxtapanodal domains. These observations, coupled with improved conduction velocity of the remyelinated axons (**Figure 3(i)–(m)**), indicate that a relatively mature pattern of ion channel organization is recapitulated within spinal cord axons remyelinated by transplanted OECs.

TRANSPLANTATION OF OLFACTORY ENSHEATHING CELLS INTO EXPERIMENTAL SPINAL CORD TRANSECTION LESIONS

Local sprouting can occur after axonal transection in the mammalian spinal cord, but the axons do not regenerate for an appreciable distance. However, experimental approaches have been reported to improve elongative regeneration of axons in the transected mammalian spinal

cord. These approaches include blockade of inhibitory proteins on glial cells and introduction of neurotrophic factor-enhanced peripheral nerve bridges. In a large number of recent studies, OECs have been transplanted into injured spinal cord and significant functional recovery has been reported [28–29,33,63]. The precise mechanisms accounting for this functional recovery are complex and include promotion of axonal regeneration, remyelination, neuroprotection, and induction of neovascularization. We should point out that in one study, functional improvement was not observed following OEC transplantation but was observed following Schwann cell transplantation [64]. Moreover, other investigators have not found unique migratory properties of OECs [65] and one report questioned the efficacy of transplantation of lamina propria into complete spinal cord transection [66].

OECs transplanted into the dorsal hemisected spinal cord survive and integrate into the lesion (**Figure 4**). **Figure 4(a)** shows a sagittal section of the spinal cord

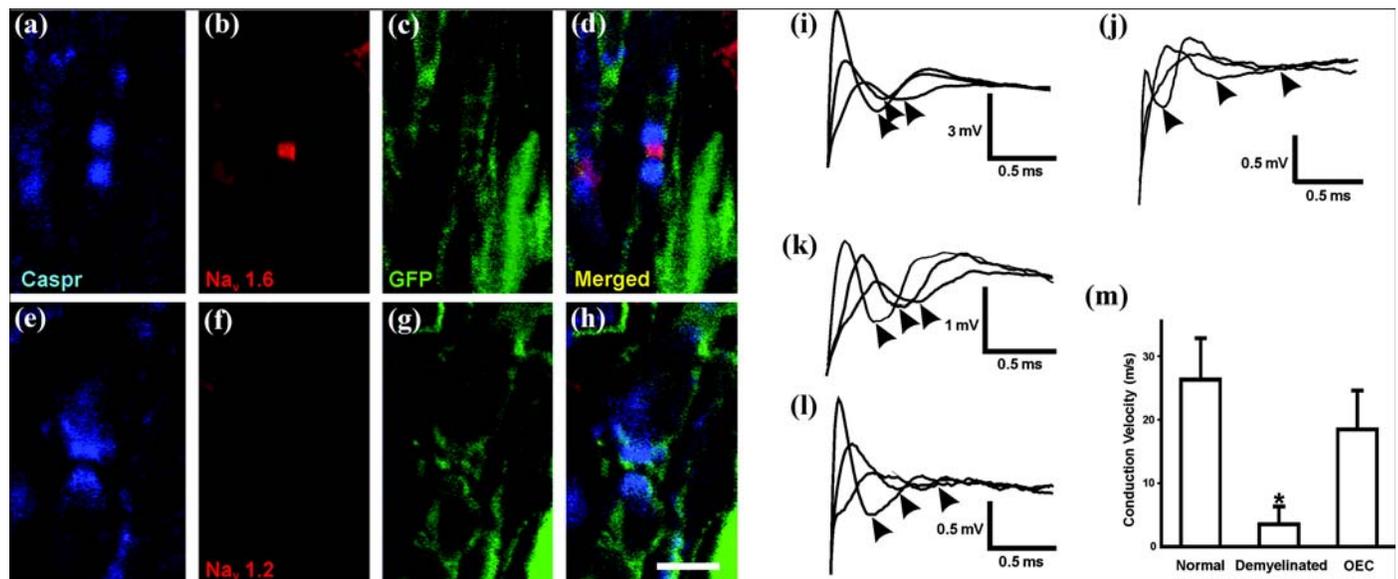


Figure 3.

Histological and electrophysiological evidence of mature node formation 3 weeks after olfactory ensheathing cell (OEC) transplantation into chemically demyelinated lesion. **(a)–(h)** Nodes of Ranvier associated with green fluorescent protein (GFP)-OECs (green) double-stained with contactin-associated protein (Caspr) (blue, stains in paranodal regions) and either **(a)–(d)** voltage-gated sodium channel (Na_v) 1.6 (red), commonly associated with mature nodes, or **(e)–(h)** $Na_v1.2$ (red), commonly associated with nonmyelinated axons or early stages in node formation. Merged images (**(d)** and **(h)**) show that $Na_v1.6$ is clustered at Caspr-delimited nodes, while $Na_v1.2$ is absent. **(i)–(l)** Compound action potentials recorded across lesioned area from **(i)** normal control spinal cord, **(j)** demyelinated lesion without cell transplantation, and **(k)–(l)** two OEC transplanted lesions. **(m)** Conduction velocities of normal, demyelinated only, and demyelinated and OEC-transplanted spinal cords ($n = 6$ each group). Conduction velocities for demyelinated axons significantly differ from both normal control and OEC-transplanted spinal cords ($*p < 0.005$). Scale bar is $10 \mu\text{m}$ for all photographs. Modified from Sasaki M, Lankford KL, Zemedkun M, Kocsis JD. Identified olfactory ensheathing cells transplanted into the transected dorsal funiculus bridge the lesion and form myelin. *J Neurosci.* 2004;24(39):8485–93. [\[PMID: 15456822\]](https://pubmed.ncbi.nlm.nih.gov/15456822/)

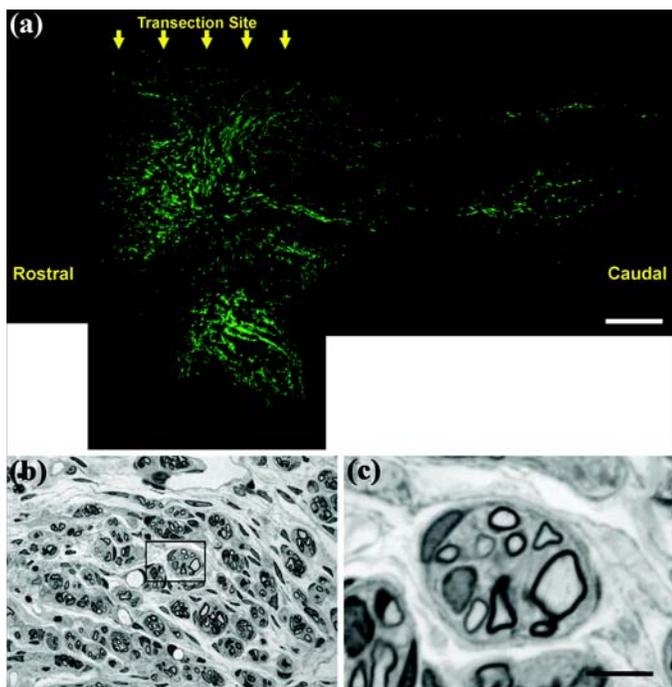


Figure 4.

Distribution and organization of olfactory ensheathing cells (OECs) transplanted into transection lesion. (a) Sagittal frozen section showing distribution of green fluorescent protein-OECs within and beyond transected lesion. (b)–(c) Semithin coronal plastic sections within lesioned area showing clusters of myelinated axons, which was characteristic of OECs transplanted in transected lesions. (b) Low magnification image showing many axon clusters. (c) Boxed area in (b) enlarged to show detail of individual axon cluster apparently surrounded by another cell. Scale bars: (a) 250 μm , (b) 30 μm , (c) 6 μm . Modified from Sasaki M, Lankford KL, Zemedkun M, Kocsis JD. Identified olfactory ensheathing cells transplanted into the transected dorsal funiculus bridge the lesion and form myelin. *J Neurosci*. 2004;24(39):8485–93. [PMID: 15456822]

spanning the transection site 4 weeks after transplantation of GFP-expressing OECs. Note that the green cells have integrated across the transection site (**Figure 4(a)**). Examination of the lesion site after transplantation in coronal section from semithin plastic embedded sections indicates groups of myelinated axons (**Figure 4(b)**). A higher power image (**Figure 4(c)**) shows that these groups of myelinated axons are surrounded by a cellular element. This configuration of myelinated regenerated axons inside of a cellular channel or bridge is unique to transplantation of OECs and is not observed after transplantation of Schwann cells [36].

Raisman proposes that two populations of cells are present in OEC preparations derived from the OB: a fibroblast-like cell, or A-cell, and a Schwannlike cell, or S-cell [35]. He proposes that the A-cell forms the surrounding cell and that the S-cells can form myelin on the regenerated axons. Moreover, the A-cell appears to form a channel across the lesion zone through which regenerating axons can grow. The myelin at this position in the lesion is primarily peripheral-like [36,63]. Endogenous Schwann cells can invade SCI sites and form myelin, and while OECs contribute to the remyelination, endogenous Schwann cells also likely contribute.

OECs can produce several molecules that may promote axonal regeneration and neuronal survival. These molecules include neurotrophic factors such as nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), and glial cell line-derived neurotrophic factor [20,67–69]. OECs have been shown to decrease spinal cord lesion size, possibly because of a local neuroprotective effect by neurotrophin release.

A recent study examined the effects of OEC transplantation into the dorsal transected spinal cord, which transects the dorsal corticospinal tract on apoptosis and neuronal death in the primary motor cortex (M1) [44]. Transection alone results in considerable apoptosis and atrophy of M1 pyramidal neurons [70]. We found that the number of apoptotic M1 neurons after corticospinal tract transection and OEC transplantation was reduced by about half at 1 week. Moreover, the number of surviving M1 pyramidal neurons was considerably increased at 4 weeks posttransection if OECs were transplanted. Interestingly, BDNF levels in the spinal cord transplant site were increased, suggesting that BDNF may have played a neuroprotective role in preserving the transected cortical neurons [44]. Thus, in addition to axonal regeneration and remyelination, OECs may provide trophic support for both local and remote neuronal survival.

POSSIBLE CONTRIBUTION OF OLFACTORY ENSHEATHING CELL TRANSPLANTATION TO PERIPHERAL NERVE REPAIR

Unlike the CNS, regeneration can occur in the PNS. The Schwann cells in the distal segment of a cut nerve dissociate from the degenerating axons, upregulate p75NGFR, and express NGF [71]. The axons in the proximal nerve stump sprout and regenerate through Schwann

cell-enriched basal lamina tubes and can reestablish functional connections in peripheral targets such as skin and muscle; various degrees of functional recovery can occur. However, issues such as navigation of axons across a complex nerve injury site and appropriate targeting to peripheral end structures are major clinical concerns.

OEC transplantation has also been considered for enhancing repair of peripheral nerve fibers. The rationale is that OECs may provide a scaffold for the regenerating axons, as well as trophic factors and directional cues [72]. Transplantation of OECs into axotomized facial nerve has been shown to enhance axonal sprouting [72–73] and promote the recovery of vibrissae motor performance [74]. Choi and Raisman demonstrated that the rate of eye closure increased after OEC transplantation in a facial nerve lesion model but that aberrant nerve branching was unchanged [75]. Schwann cells [76] and OECs [77] transplanted into transected sciatic nerve integrate into the injury site and form peripheral myelin on the regenerated axons. Moreover, the nodes of Ranvier of the regenerated axons myelinated by the transplanted cells express the appropriate sodium channel ($\text{Na}_v1.6$). Whether these engrafted cells accelerate or improve functional outcome after nerve injury is yet to be determined [77].

ONGOING CLINICAL STUDIES USING OLFACTORY ENSHEATHING CELLS IN SPINAL CORD INJURY

Several groups are conducting or planning clinical studies on OEC transplantation into patients with SCI [78–80]. Feron and colleagues have conducted a phase I safety study using suspensions of OECs cultured from biopsied tissue from the patients' own OM, thus reducing immune rejection [81]. They reported no adverse effects at 12 months posttransplantation but no neurological improvement. Lima and colleagues (Egas Moniz Hospital, Lisbon, Portugal) described a treatment in which they packed the cavity of the SCI site with acutely prepared minced OM tissue, which includes many cell types, including stem cells and OECs. They reported that the OM autograft transplantation was safe and potentially beneficial, but efficacy was not clearly established [82].

In studies by Huang and colleagues (Chaoyang Hospital, Beijing, China), several hundred patients have received transplants of cultures from human embryonic OBs obtained from 14 to 16 fetuses [83–85]. Some func-

tional improvement was reported as early as 1 day after transplantation. Surely such an early effect is not the result of axonal regeneration or remyelination. One should note that the Lima et al. and Huang et al. studies did not include control studies [78,84].

Dobkin et al. independently studied seven patients with chronic SCI who were undergoing surgery by the Huang group in Beijing [84]. For assessment, they used magnetic resonance imaging, the protocol of the American Spinal Injury Association for change in disability, and a detailed history of the perioperative course. They concluded that the phenotype and fate of the cells referred to as OECs are unknown and that perioperative morbidity and lack of functional benefit were very serious shortcomings. They also emphasized a lack of attempt to meet international standards for safety and efficacy. On the basis of their observations, they urge physicians not to recommend this procedure to patients at this time.

Assessing the efficacy of therapeutic interventions in SCI including cell therapy approaches is difficult because some "spontaneous" functional improvement occurs in most patients with SCI [86]. Moreover, the surgical intervention necessary for transplanting cells can alone lead to modest functional improvement. Issues related to assessment methods of patients with SCI in clinical studies are currently being discussed, with an emphasis on assessing the degree of an individual patient's functional recovery [87]. Clearly, the complexity of SCI and the difficulty in accurately assessing functional recovery will be challenges for all interventional clinical studies for SCI.

While reconstruction of appropriate spinal circuits by cell-based therapies is the ultimate long-term goal of cell transplantation research, laboratory work to date suggests that more immediate therapeutic benefits will come from neuroprotective effects and remyelination. Moreover, the most extensive functional recovery in animal models of SCI with cell transplantation is for treatment of acute and subacute SCI. Early intervention may reduce scar formation and secondary cell death by causing the release of appropriate trophic factors by engrafted cells. Moreover, angiogenic factors released by transplanted cells could cause neovascularization, which would be critical for tissue preservation. Some demyelination in patients with long-term (a decade) SCI has been reported [88]. If long-term SCI patients preserve some long tract axons in the spinal cord that were demyelinated, remyelination of these tracts by cell transplantation could cause some functional improvement. An important remaining challenge

for cell-based therapies in SCI is determination of the optimal cell type, method of delivery, and timing of cellular intervention.

CONCLUSIONS

OECs are unique glial cells that support axonal growth of olfactory nerve fibers into the OB of the CNS. They form cellular “channels” through which axons can grow, produce a number of neurotrophic factors, and under special conditions, can form peripheral-like myelin on axons. In experimental SCI models, including transection and contusion injuries, transplantation of OECs within a week after injury can improve functional recovery. Some functional improvement was reported when OECs were transplanted several months after injury. While the precise mechanisms for the therapeutic effects of OECs are not fully understood, several studies indicate that facilitation of axonal regrowth, remyelination, and neuroprotection may contribute. Clinical studies using OECs in SCI are ongoing, but efficacy has not as yet been established in these initial studies [84]. To date, the clinical studies have been performed in patients with chronic SCI, but experimental studies suggest that OECs are most effective in acute and possibly subacute SCI. Evaluating the therapeutic potential of OECs in acute SCI will be important in future clinical studies.

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