Table 1 Details of all primary antibodies.

Primary antibodies	Target	Host	Code/clone	Dilution
A2B5-Biotin	Oligodendrocyte	Mouse	105-HB29	1/10
BrdU	Mitosis	Mouse	BMG6H8	1/10
GFAP	Astrocyte	Mouse	GA5	1/300
GFAP	Astrocyte	Rabbit	N1506	1/2
GFP	GFP protein	Goat	ab5450	1/500
GLAST	Transporter	Rabbit	ab85863	1/300
GLAST-APC	Transporter	Mouse	ASCA-1	1/10
ICAM1	Horizontal basal cell	Mouse	1A29	1/200
ICAM1-PE	Horizontal basal cell	Mouse	1A29	1/10
IgG1-FITC	Control	Mouse	MOPC-21	1/10
IgG1-PE	Control	Mouse	11711	1/10
IgG2a-APC	Control	Mouse	S43.10	1/10
IgM-Biotin	Control	Mouse	IS5-20C4	1/10
krox20	Schwann cell	Rabbit	ab43020	1/50
MAP2	Neuron	Rabbit	ab32454	1/200
MBP	Oligodendrocyte	Mouse	ab62631	1/200
Nestin	Neural stem cell	Rabbit	NBP1-02419	1/200
Neurofilament	Axon	Rabbit	C28E10	1/100
NG2	Oligodendrocyte	Rabbit	AB5320	1/200
NG2-FITC	Oligodendrocyte	Mouse	LHM-2	1/10
O4	Oligodendrocyte	Mouse	MO15002	1/200
olig2	Oligodendrocyte	Sheep	ab85900	1/200
$p75^{NTR}$	OEC	Rabbit	ab52987	1/50
PDGFRα	Oligodendrocyte	Rabbit	ab61219	1/200
Peripherin	Axon	Chicken	ab39374	1/100
P0	Schwann cell	Rabbit	ab31851	1/200
RIP	Oligodendrocyte	Rabbit	D94C12	1/100
S100β	Schwann cell	Rabbit	ab41548	1/500
sox10	Schwann cell	Rabbit	ab64055	1/200
Tuj1	Neuron	Mouse	TU-20	1/200

The inner and outer diameters of the silicone tube were 2 and 3 mm, respectively. The stumps of the left saphenous nerve were placed in a silicon tube containing type IA collagen gel plus EGFP-positive olfactory sphere cells (2.5×10^4 cells/μl). All rats received subcutaneous cyclosporine (10 mg/kg) and gentamicin (8 mg/kg) daily for the next 7 days. Rat tissues were examined 2 weeks post-transplantation. The saphenous nerves were fixed in 4% PFA overnight, cryoprotected in 30% sucrose, embedded in OCT compound, and frozen. Sections (10-μm-thick) were axially cut from the blocks using a cryostat.

The mean axial areas in the midpoint of the regenerated saphenous nerves with and without OS cells were recorded and measured on the cross-sectional DAPI-positive areas using image analysis software (Image J, version 1.44; http://rsbweb.nih.gov/ij/index.html). Saphenous nerves with (n = 8) and without OS (n = 4) cells were analyzed.

Assessment of locomotor behavior

Hind limb locomotor function was assessed weekly after SCI and transplantation using an open-field walking test. Two examiners who were blinded to the treatments observed the hind limb movements and scored locomotor function according to the Basso, Beattie, and Bresnahan (BBB scale, which ranges from 0 (paralysis) to 21 points (normal gait).

Immunohistochemistry

Sections were stained with anti-ICAM-1 (1:200 mouse monoclonal antibody; Abcam), anti-chondroitin sulfate proteoglycan 4 (NG2, 1:200 rabbit polyclonal antibody; Millipore, Billerica, MA), anti-Olig2 (1:200 sheep polyclonal antibody; Abcam), anti-EAAT1 (GLAST; glutamate–aspartate transporter; 1:300 rabbit polyclonal antibody; Abcam), anti-GFP (1:500 goat polyclonal antibody; Abcam), anti-neurofilament-L (NF, 1:100 rabbit monoclonal antibody; Cell Signaling Technology), anti-Olig2 (1:200 sheep polyclonal antibody; Abcam), anti-p75 NGFR (1:50 rabbit monoclonal antibody; Abcam), anti-peripherin (1:100 chicken polyclonal antibody; Abcam), anti-EGR2 (krox20, 1:50 rabbit polyclonal antibody; Abcam), anti-SOX10 (1:200 rabbit polyclonal antibody; Abcam), anti-Myelin Basic Protein (1:100 rabbit polyclonal antibody; Abcam), anti-Myelin Protein Zero (1:100 rabbit polyclonal antibody; Abcam), and anti-S100β (1:500 rabbit polyclonal antibody; Abcam). The secondary antibodies used were DyLight 488-conjugated goat anti-mouse antibody (1:200; KPL), Alexa Fluor® 650 donkey anti-mouse antibody (1:200; Abcam), DyLight 549-conjugated goat anti-rabbit antibody (1:200; KPL), DyLight 594-conjugated donkey anti-rabbit antibody (1:200; Abcam), DyLight 488-conjugated donkey anti-goat antibody (1:200; Abcam), DyLight 594-conjugated goat anti-chicken antibody (1:200; Abcam) and

Cy5-conjugated donkey anti-sheep antibody (1:200; Jackson ImmunoResearch). The slides were counterstained with DAPI (Vector Laboratories, Burlingame, CA). Sections were assessed from images captured using a confocal laser fluorescence microscope.

Statistical analyses

Data were analyzed using one-way analysis of variance (ANOVA). For significant F ratios, the Tukey post-hoc test was performed. The level of significance was defined as $P < 0.05$, and data are presented as the mean ± SD unless otherwise indicated. Data are from at least 3 experiments.

Results

HBCs in the olfactory epithelium express oligodendrocyte precursor markers

HBCs are arranged in the olfactory mucosa as a flattened monolayer adherent to the basal lamina and express cell surface ICAM-1 (Carter et al., 2004). Using immunofluorescence staining, we found that rat HBCs co-expressed ICAM-1, NG2, and PDGFRα (Figs. 1A,C). NG2 and Olig2 (Marshall et al., 2005; Lu et al., 2000) were also co-expressed in HBCs (Fig. 1B). Except for HBCs, we could not detect the expression of NG2, Olig2 and PDGFRα in the olfactory epithelium. GLASTs, which are not expressed by brain NG2 cells (Furuta et al., 1997), colocalized with ICAM-1 and Olig2 in HBCs (Figs. 1D,E). The presence of cytoplasmic Olig2 (Fig. 1B) and the expression of GLAST (Fig. 1D) are typical features of astrocytes or astrocyte-engaged progenitors (Cassiani-Ingoni et al., 2006; Setoguchi and Kondo, 2004; Walz, 2000).

Next, we investigated whether the same populations of HBCs express OPC and astrocyte markers. We dissociated olfactory mucosa into single cell suspensions using an enzymatic procedure and separated GLAST-positive and -negative cells using MACS. FACS analysis detected weak expression of NG2 by GLAST-positive cells, and GLAST-negative cells expressed NG2 very weakly (Fig. 1H). These data indicate that HBCs express OPC and astrocyte markers.

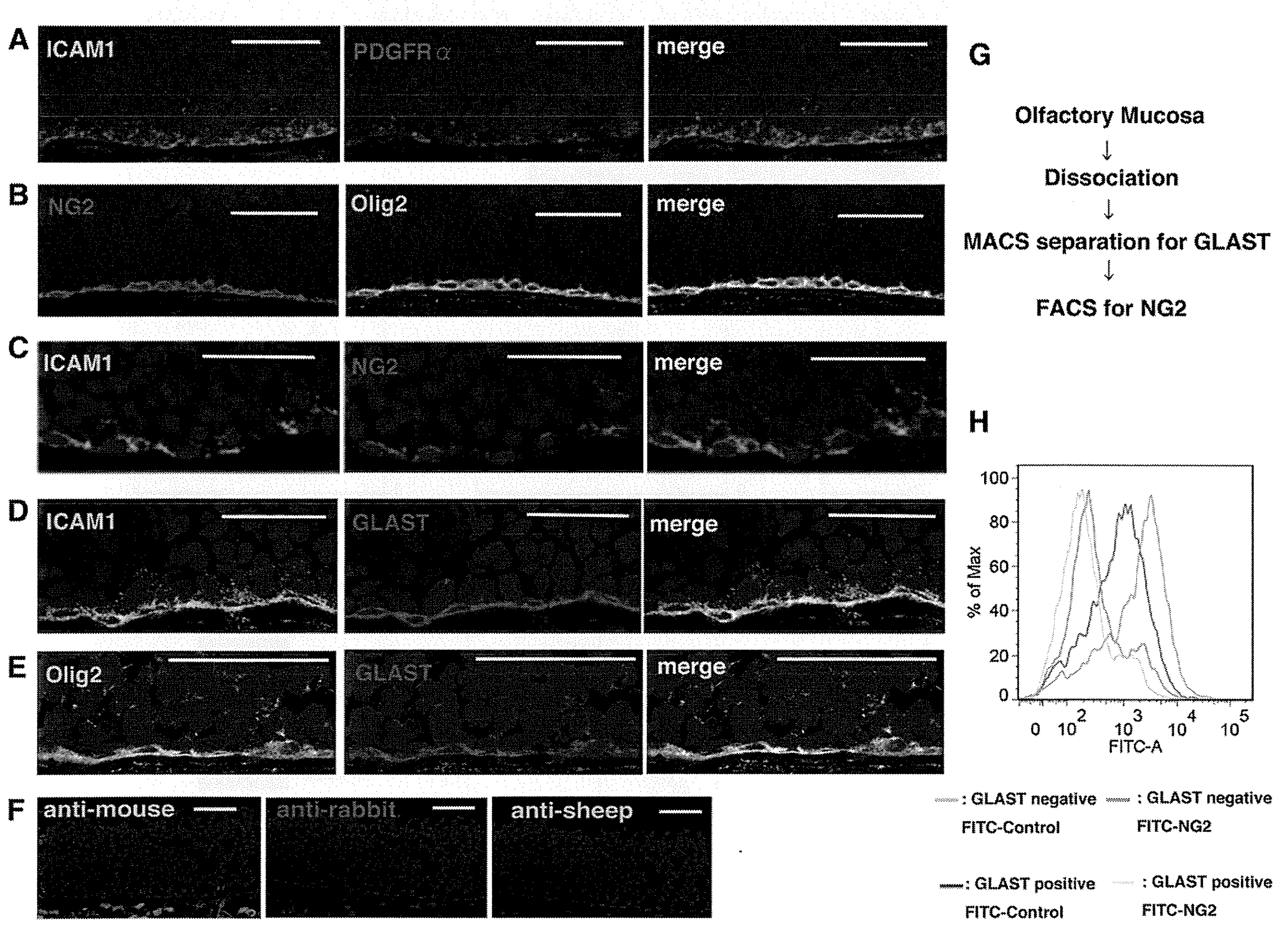


Figure 1 Immunohistochemical analysis of the HBC layer in adult olfactory epithelium. Colocalization of ICAM-1 with (A) PDGFRα, (C) NG2, and (D) GLAST. (B, E) Cytoplasmic Olig2 colocalizes with NG2 and GLAST. (F) Secondary antibody-only control to assess background staining. (G) The procedure used to investigate whether the same populations of HBCs express NG2 and GLAST by MACS following FACS. (H) Histogram of fluorescence intensity shows that GLAST-positive (sky blue, red) and -negative (orange, green) cells are weakly or very weakly positive for NG2 (sky blue, orange), respectively. Unstained cells were used for background determination (red, green). Scale bars = 50 μm for A–F.

OSs express oligodendrocyte precursor and astrocyte markers

We used a serum-free culture method to generate OSs from adult rat olfactory mucosal cells. Spheres were apparent after 3 or 4 days in culture, and they increased in size and formed aggregates after approximately 8 days. Cell clusters were classified as spheres if they were spherical in shape and had a diameter of at least 50 μm. OS cells were positive for ICAM-1, NG2, Olig2, PDGFRα, and nestin as observed using immunofluorescence staining (Fig. 2A). FACS analysis detected ICAM-1-positive OS cells that were weakly positive for GLAST and NG2 (Fig. 2B). The GLAST-positive and weakly-positive fraction was 72.02% of the cells observed (subset 1 + subset 2) (Fig. 2C), and the NG2-positive and -weakly-positive fraction was 72.37% (subset 1 + subset 2) (Fig. 2D). The GLAST- and NG2-positive fraction were 3.12% (subset 1) and 1.37% (subset 1), respectively. The majority of OS cells were weakly positive for GLAST and NG2. OPCs are often identified by A2B5 (Raff et al., 1983; Espinosa de los Monteros et al., 1993; Baracskay et al., 2007). Combinatorial FACS analysis showed that 23.5% of OS cells were double-positive for GLAST and A2B5, while 7.48% did not stain (Fig. 2E). The A2B5-positive fraction was 28.44%, and 8.01% of OS cells did not stain. The GLAST-positive fraction was 4.86%, and 1.54% did not stain. These results indicate that OS cells include a subpopulation that expresses OPC and astrocyte markers.

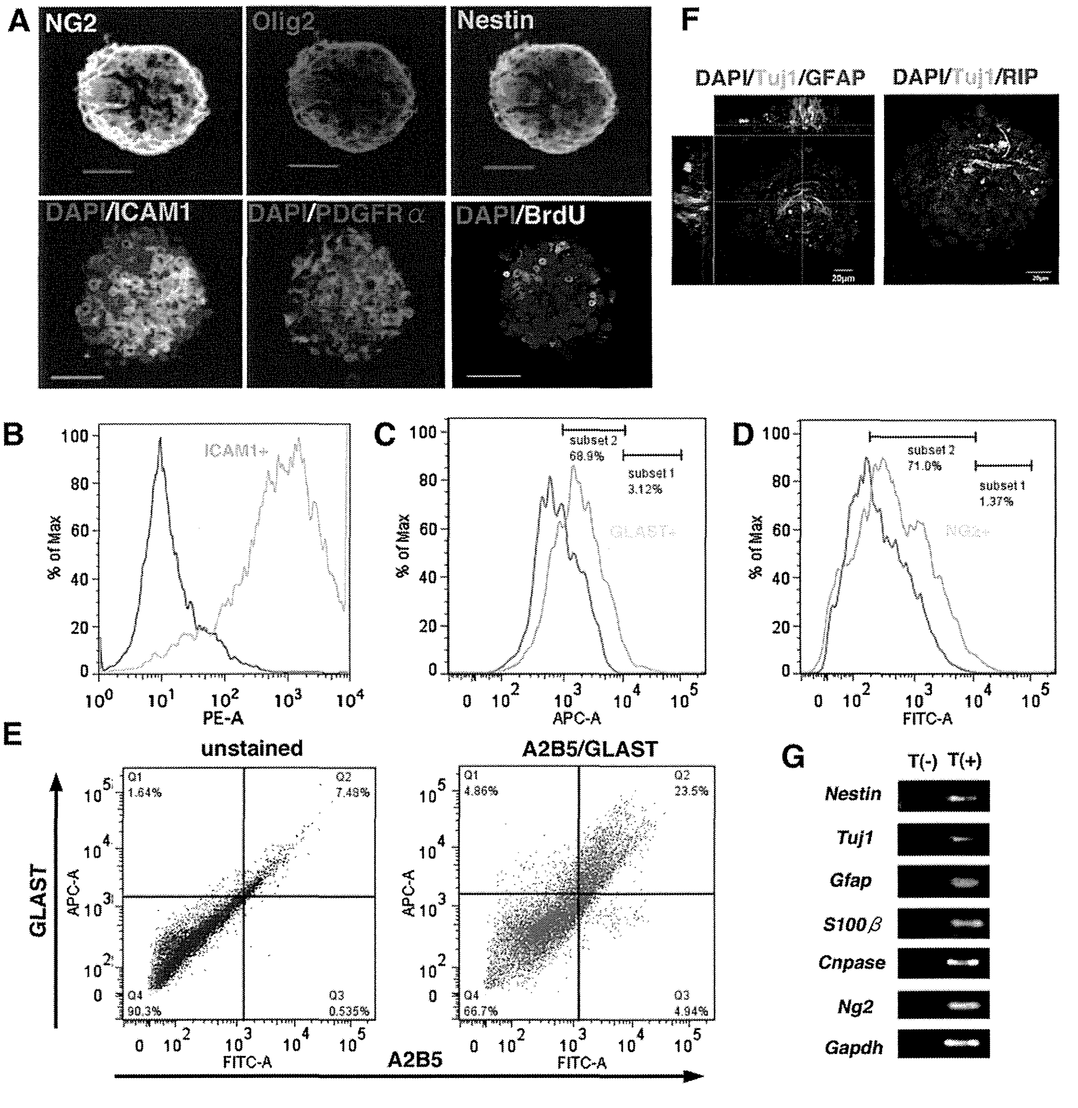


Figure 2 In vitro differentiation of OSs. (A) OSs express oligodendrocyte progenitor markers and a neural stem cell marker. OSs exhibited BrdU staining at the inner and outer parts of spheres. (B–D) Histograms of PE, APC, and FITC-fluorescence emission show that OS cells were positive for ICAM-1, and weakly positive for GLAST and NG2. (E) Combinatorial FACS analysis shows that OS cells include A2B5 + GLAST+ and A2B5 + GLAST-populations. Unstained cells were used for background determination. (F) OSs in differentiation cultures are positive for RIP and weakly positive for GFAP and Tuj1. (G) RT-PCR analyses show that OSs in the differentiation cultures express *Gfap*, *S100β*, *Cnp*, and *Ng2*, but weakly express *Tuj1* and *Nes*. T(−), no template; T(+), template presence. Scale bars = 50 μm for A, 20 μm for F.

OS cells differentiate to oligodendrocytes in vitro

OSs derived from autonomously differentiating cultures were immunopositive for RIP (marker of differentiated oligodendrocytes) (Friedman et al., 1989) and GFAP, but weakly positive for Tuj1 (Fig. 2C). RT-PCR analyses showed that OSs in the differentiation cultures expressed *Gfap*, glial-derived *S100β*, the oligodendrocyte marker gene 2′,3′-cyclic-nucleotide 3′-phosphodiesterase (*Cnp*) (Kim et al., 1984; Watanabe et al., 2006) and *Ng2*, but only weakly expressed *Tuj1* and *Nes* (Fig. 2D). *S100β* is expressed by astrocytes and Schwann cells, as well as by OPCs and oligodendrocytes (Cahoy et al., 2008).

Although human and rodent OSs express nestin, O4, Tuj1, and GFAP (Murdoch and Roskams, 2008; Tome et al., 2009), quantitative analyses of differentiated OSs have not been performed, to our knowledge. In our dissociated cultures, OS cells were positive for cytoplasmic Olig2, nuclear Olig2, or both. Olig2 expression was detected in the nuclei of 67.4 ± 9.8% of the cells, 4.4 ± 1.9% were GFAP-positive, and 9.5 ± 3.1% were MAP2-positive (Fig. 3). OS cells were weakly positive for GFAP, MAP2, and Tuj1 (Fig. 3). Most nuclear Olig2-positive cells co-expressed O4 (Fig. 3), and were positive for RIP (Fig. 3). Some RIP-positive cells exhibited a branched morphology (Fig. 3).

OS cells generate (Wang et al., 2011; Lindsay et al., 2013) OEC marker p75-positive cells (Au and Roskams, 2003; Jani and Raisman, 2004; Li et al., 1997). Here, p75 was not detected in OS cells (Fig. 3). Cell proliferation was estimated using BrdU, an analog of thymidine that is incorporated during DNA synthesis. OSs were stained by BrdU at the inner and outer parts of the spheres (Fig. 2A). BrdU was incorporated by 6.7% ± 2.9% of the OS cells (Fig. 3). They represent oligodendrocyte progenitors at an early stage of differentiation in vitro.

OS cells differentiate into oligodendrocytes in vivo

We tested the potential of OS cells to differentiate into oligodendrocytes, astrocytes, and neurons in the injured rat spinal cord. EGFP-positive OS cells were transplanted into wild-type adult male rats 9 days after inflicting a thoracic spinal contusion. After transplantation, animals were monitored for locomotor activity and euthanized 4 weeks after transplantation for histological examination. BBB-scale scores throughout the 37-day period of the experiment are

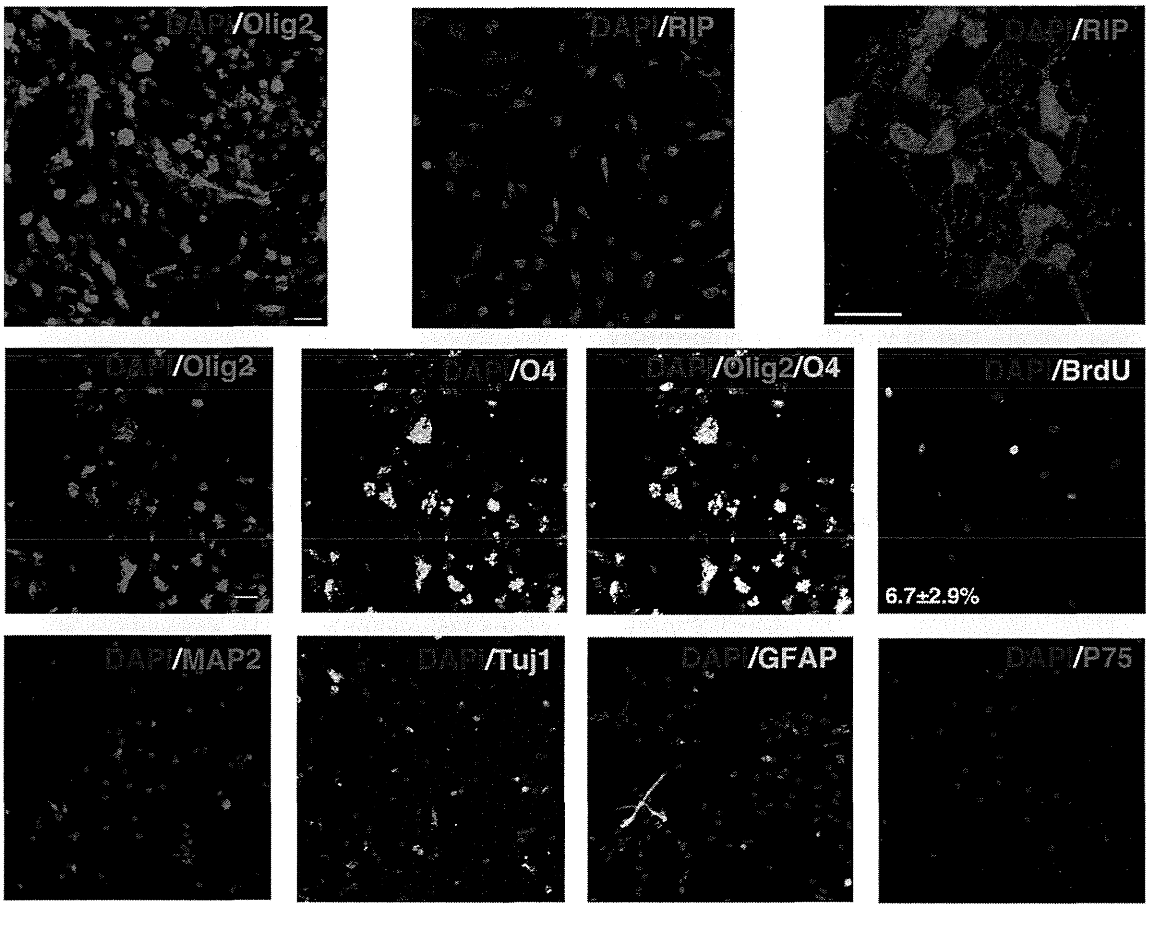


Figure 3 In vitro differentiation of OS cells. OS cells were positive for Olig2, O4, and RIP, but weakly positive for GFAP, MAP2, Tuj1 and P75. BrdU was incorporated by 6.7 ± 2.9% (mean ± SD) of OS cells. The percentage represents the mean ± SD of 3 independent experiments. Scale bars = 20 μm.

shown in Fig. 4. These data demonstrate partial recovery at 4 weeks. In the first week after SCI, all rats lacked movement in the 3 hind-limb joints (BBB scale score of 0 or 1). The BBB-scale scores in non-treated (injury only) rats improved from 0.6 ± 0.5 (mean ± SD) before transplantation to 1.6 ± 1.1, 5.3 ± 0.5, 6.3 ± 0.5, and 7.3 ± 0.5 at 1, 2, 3, and 4 weeks after transplantation, respectively (n = 3). The BBB scale scores in vehicle-treated rats improved from 0.3 ± 0.5 (mean ± SD) before transplantation to 3.3 ± 1.5, 5.3 ± 1.5, 7.3 ± 0.5, and 8.3 ± 0.5 at 1, 2, 3, and 4 weeks after transplantation, respectively (n = 4). Rats treated with OS cells showed an improvement in BBB scale scores from 0 before transplantation to 0, 2.6 ± 0.5, 7.6 ± 0.5, 10.0 ± 1.0, and 11.0 ± 1.0 at 1, 2, 3, and 4 weeks after transplantation, respectively (n = 5). The difference in locomotor function between non-treated rats and rats treated with vehicle was not statistically significant ($P > 0.1$), but was in rats treated with OS cells and vehicle was statistically significant at 3 and 4 weeks post-transplantation ($P < 0.05$).

OS cells integrated within the host white matter and extended elongated processes parallel to the axons in a rostrocaudal direction. EGFP-positive cells associated closely with neurofilament protein (Fig. 5A). EGFP-positive cells were immunopositive for cytoplasmic and nuclear Olig2 (Figs. 5G,H, K–M), and RIP (Figs. 5P–R). Nuclear-Olig2-positive cells exhibited a multi-processed morphology (Figs. 5I,N,S). Myelin basic protein (MBP) is expressed in both mature and immature myelin sheath (Fitzner et al., 2006; Simons and Trotter, 2007). OS cells extended GFP-positive processes, which co-localized with MBP (Figs. 5E,J).

NG2, GFAP and MAP2 were not detected by their cognate antibodies in EGFP-positive cells (Fig. 5F), and p75 was undetectable in transplanted OS cells (Fig. 5B). Some OPCs express the peripheral myelin-associated (P_0) proteins and P_0 rings, as a Schwann cell marker in vivo (Zawadzka et al., 2010). Transplanted OS cells presented weak positive for P_0 proteins, but not P_0 ring (Figs. 5O,T). Microglial cells do not express Olig2 (Kuhlmann et al., 2008; Tatsumi et al., 2008). These findings indicate that in vivo OS cells differentiate into myelinating oligodendrocytes, but not into astrocytes, neurons, OECs, Schwann cells, or microglia.

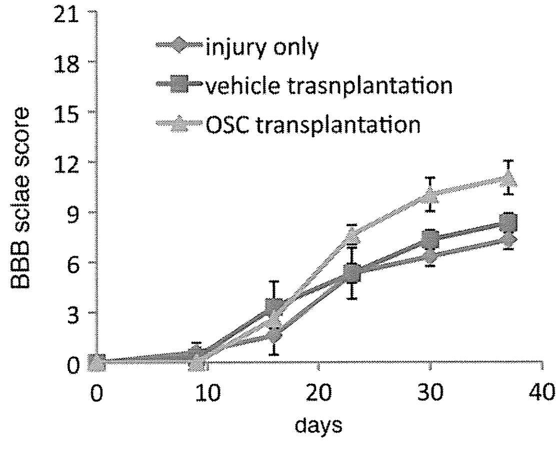


Figure 4 Time course of recovery of hind limb function after SCI. OS cells and vehicle were transplanted into the SCI epicenter 9 days after injury. Transplantation of OS cells resulted in functional recovery.

OS cells also differentiate into Schwann cells in vivo

Next, we examined the differentiation of OS cells transplanted into regenerating transected saphenous nerves. HBCs are involved in the regeneration of olfactory sensory neurons. Therefore, for the regeneration experiments in peripheral nerves, we chose the saphenous nerve as the sensory nerve. A 10-mm gap was introduced into the nerves, and the nerve ends were encased in silicone tubes containing collagen gel alone (n = 9) or collagen gel and OS cells (n = 9). Regeneration was expressed as the percentage closure of the 10-mm gap. We found that the gaps between the proximal and distal stumps were 100% and 55% closed in tubes containing or lacking OS cells, respectively. Axial areas in the midpoint of regenerated nerves with and without OS cells were 113.2 ± 38.9 mm^2 and 25.9 ± 1.7 mm^2, respectively.

Compared to nerves regenerating in the presence of OS cells, nerves regenerating in the absence of OS cells were thinner (Figs. 6A,F) and had smaller cross-sectional DAPI-positive areas (Figs. 6B,C,G,H). Peripherin (Yuan et al., 2012) expression was observed in all regenerating nerves (Figs. 6D,I), whereas Krox20 (Topilko et al., 1994; Ghislain et al., 2002) was expressed in nerves treated with OS cells (Figs. 6E,J). EGFP-positive cells were also positive for Krox20, Sox10 (Bremer et al., 2011), and S100β (Figs. 6K,M,N), but not peripherin (Fig. 6L). EGFP-positive cells co-localized with P_0 proteins and presented P_0 rings (Figs. 6O–Q). These data show that OS cells undergo Schwann-cell differentiation.

Discussion

Olfactory sphere generation

Various culture conditions generate OSs (Zhang et al., 2004; Murrell et al., 2005; Barraud et al., 2007; Murdoch and Roskams, 2008; Tome et al., 2009; Krolewski et al., 2011) that differ according to species (human, rat, mouse), developmental stage (embryo, neonatal, adult), presence of serum, chemicals, and trophic factors. Here we used a serum-free culture method to generate OSs from adult rat olfactory mucosal cells.

OSs are derived from the olfactory epithelium or lamina propria (Barraud et al., 2007; Krolewski et al., 2011; Toft et al., 2012; Lindsay et al., 2013). Rat embryonic olfactory mucosa generates 2 distinct types of spheres (Tome et al., 2009) as follows: mesenchymal-like OS cells from the lamina propria, and epithelial-like OS cells from the olfactory epithelium. Mesenchymal-like OS cells were also generated from human lamina propria (Lindsay et al., 2013).

Differentiated OS cells expressed p75 in vitro (Barraud et al., 2007; Wang et al., 2011; Lindsay et al., 2013). Mesenchymal-like OS cells express p75, but not epithelial-like OS cells in vitro (Lindsay et al., 2013). In this study, OS cells were not positive for p75. This difference may be due to culture conditions. Our OS cells comprised heterogeneous subpopulations, but predominantly epithelial-like stem cells.

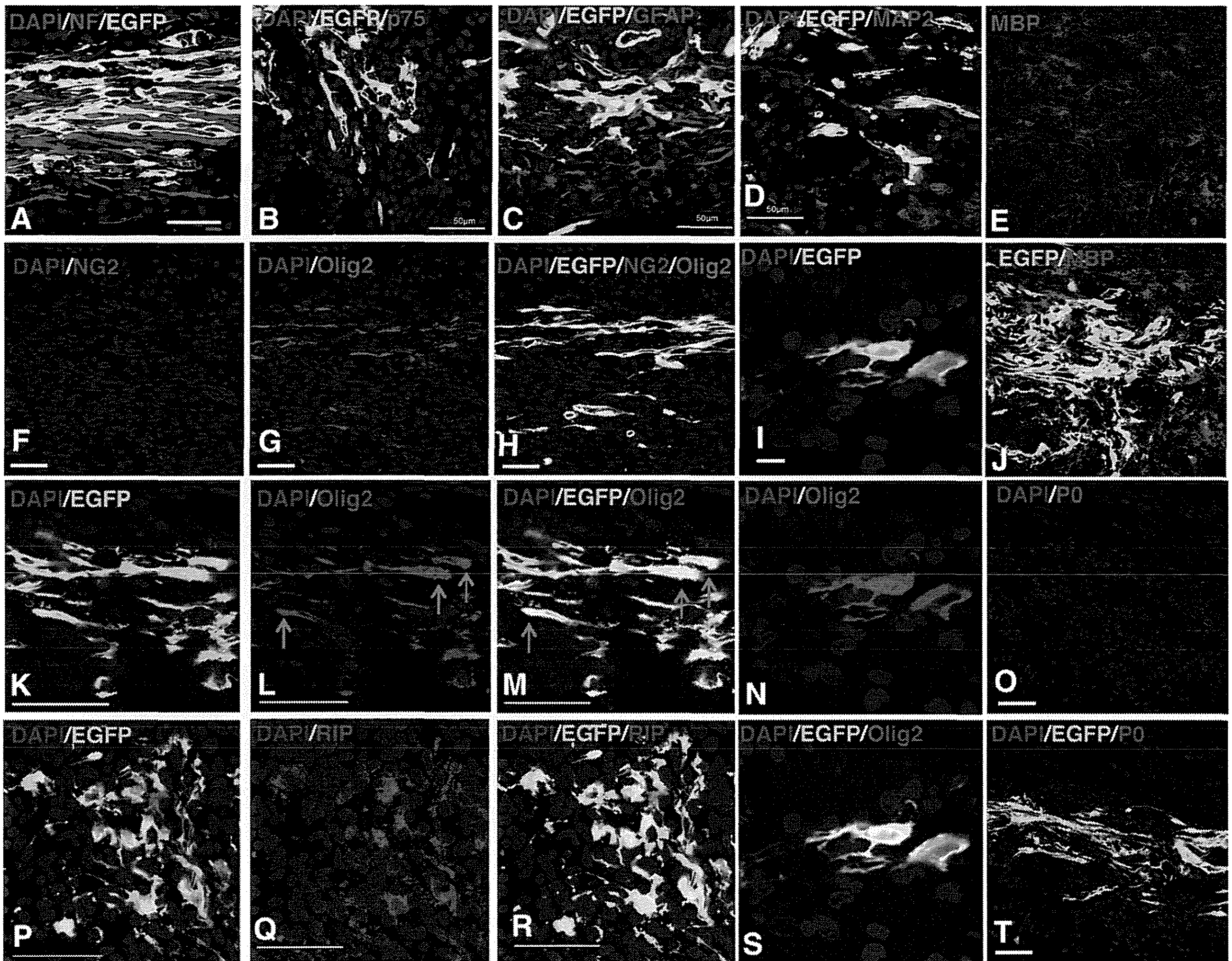


Figure 5 Transplantation of OS cells into injured spinal cords. Photomicrographs of a longitudinal section shows OS cells integrated into the host parenchyma. (A) EGFP-positive cells closely associated with neurofilament protein. (B–D) EGFP-positive cells did not colocalize with p75, GFAP, or MAP2. (F–H) EGFP-positive cells express Olig2 but not NG2. EGFP-positive cells express nuclear olig2 (K–M) and RIP (P–R). Pink arrows indicate the nuclear localization of Olig2. (I, N, S) EGFP and nuclear Olig2 double-positive cells exhibit multiprocessed morphology. (E, J) OS cells extend GFP-positive processes, which co-localize with MBP. (O, T) OS cells were weakly positive for P_0 proteins. Scale bars = 50 μm.

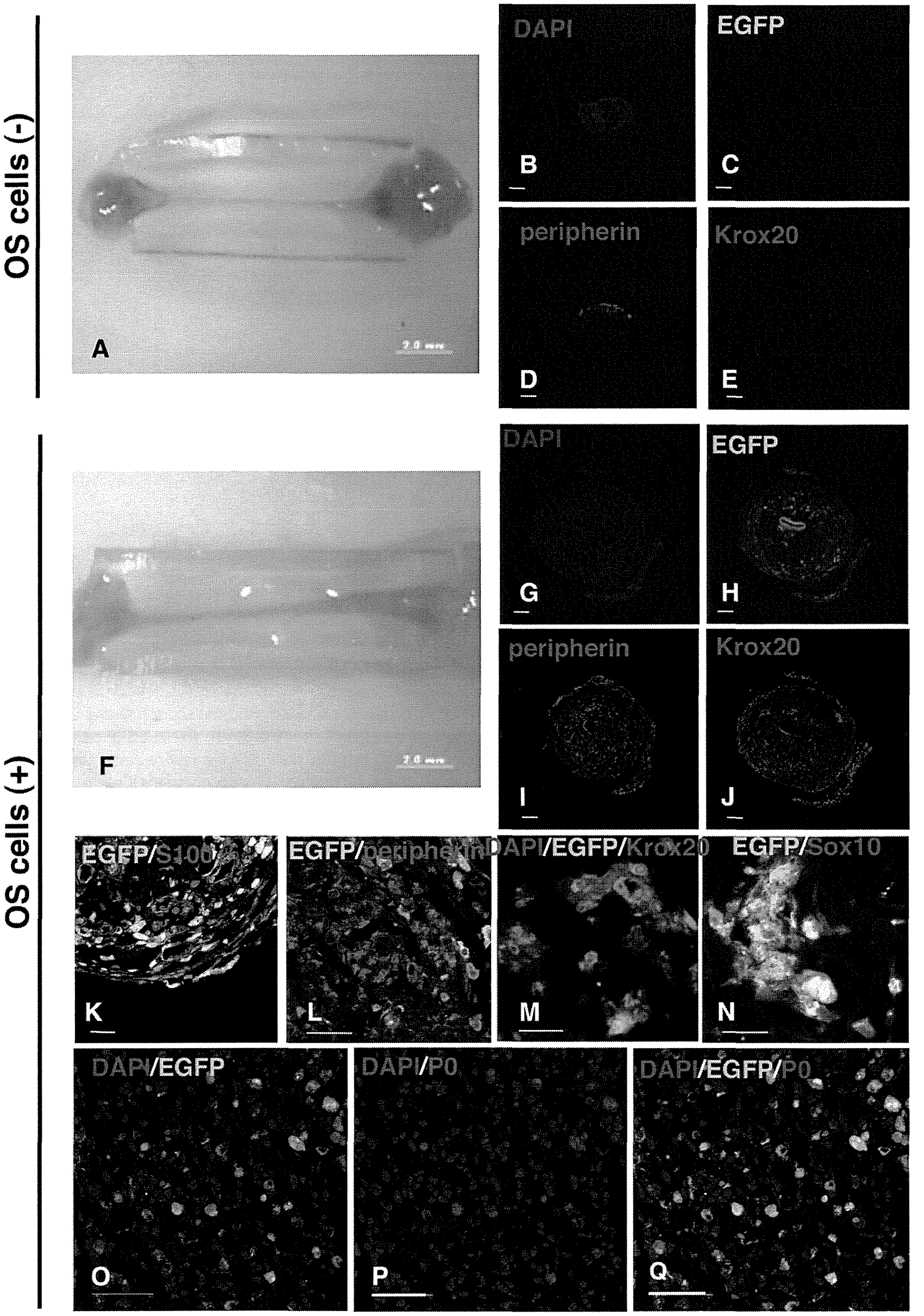
OS cells differentiated into oligodendrocytes

Cytoplasmic Olig2 is a marker of astrocyte progenitors. In brain injury, the fate choice for astrocytes is associated with cytoplasmic or nuclear Olig2 localization (Magnus et al., 2007; Tatsumi et al., 2008; Zhao et al., 2009). OPCs generate a subpopulation of astrocytes in addition to oligodendrocytes (Zhu et al., 2008). The study of Komitova et al. (2011) suggests that OPCs are not a major source of reactive astrocytes in the neocortex. OPCs can be identified by the expression of NG2, PDGFRα, and A2B5. A2B5-positive OPCs are referred to as O2A cells because they produce oligodendrocytes in serum free-medium and type 2 astrocytes in serum-containing medium in vitro (Raff et al., 1983). GLAST expression is a marker for astrocytes.

In the present study, OS cells expressed NG2, PDGFRα, A2B5, and GLAST. Interestingly almost all OS cells were positive for nuclear Olig2, O4, and RIP in vitro. Some

Figure 6 Transplantation of OS cells into transected saphenous nerves. Regenerating nerves from the same animal are shown. The nerve regenerating in the collagen gel-containing silicone tube is thinner than the nerve regenerating in the presence of collagen and olfactory sphere cells (A, F). Nerves regenerating in the absence of OS cells have smaller cross-sectional DAPI-EGFP-positive areas (B, C, G, H). Peripherin was observed in regenerating nerves (D, I). Krox20 is expressed in nerves treated with OS cells (E, J). EGFP-positive cells are positive for Krox20, Sox10 and S100β, but not peripherin (K–N). EGFP-positive cells co-localize with P_0 proteins and form P_0 rings (O–Q). OSCs: olfactory sphere cells. Scale bars = 2 mm for the upper panels, 50 μm for the middle panels and 20 μm for the lower panels.

transplanted GFP-positive OS cells expressed cytoplasmic Olig2, GFAP, and Tuj1. At the onset of remyelination, markers of both OPCs and oligodendrocytes can be identified, but not NG2 and GFAP (Fancy et al., 2004). Here, transplanted EGFP- and nuclear Olig2-double-positive cells exhibited multiprocessed morphology characteristic of differentiated



oligodendrocytes. Transplanted OS cells were positive for RIP and MBP, but not NG2 and GFAP. These findings indicate that OS cells differentiated into oligodendrocytes, but not into astrocytes in vitro and in vivo.

OPC transplantation: comparison with previous studies

Transplanted OPCs differentiate into oligodendrocytes upon transplantation in SCI (Bambakidis and Miller, 2004; Lee et al., 2005). In a study of SCI rats with moderate midthoracic contusions, BBB scale scores of 9 and 10 were obtained 2 and 4 weeks after OPC transplantation, respectively (Lee et al., 2005). In another study, rats with similar SCIs had BBB scale scores of 13 and 18 at 2 and 4 weeks after OPC transplantation, respectively (Bambakidis and Miller, 2004). No significant differences were observed in locomotor function of the transplanted versus non-transplanted rats in either of these studies 2-weeks post-transplantation. In both studies, compared with untreated animals, the function of rats transplanted with OPCs improved significantly after 4 weeks. Our midthoracic SCI rats administered vehicle had BBB scale scores of 5.3 ± 1.5 and 8.3 ± 0.5 at 2 and 4 weeks post-transplantation, respectively. Rats transplanted with OS cells had BBB scale scores of 7.6 ± 0.5 and 11.0 ± 1.0 at 2 and 4 weeks post-transplantation, respectively. At 3 and 4 weeks after transplantation, rats transplanted with OS cells function significantly better than untreated or vehicle-treated rats. Transplanted OS cells integrated within the host white matter and extended elongated processes parallel to the axons in a rostrocaudal direction. These cells were immunopositive for myelinating oligodendrocyte markers and exhibited a multiprocessed morphology. These data suggest that OS cells differentiated to myelinated oligodendrocytes and contributed to the recovery of locomotor function.

Differentiation of OS cells into Schwann cells

The rat saphenous nerve, the sensory nerve of the thigh, is commonly employed for studies of nerve regeneration in the peripheral nervous system. The nerve consists of both unmyelinated and myelinated axons with nearly 4-times as many unmyelinated axons as myelinated axons (Carter and Lisney, 1987). Silicone tubes containing various growth-enhancing substances have been used in studies of peripheral nerve regeneration, including collagen- or laminin-containing gels, Schwann cells, and various growth factors (Yannas and Hill, 2004). Collagen gels can enhance axonal regeneration by the formation of a fibrin matrix up to 10 mm in nerve tubes (Wiliams et al., 1983). Although a fibrin matrix does not form in the long axonal gap, Schwann cells can increase the bridged gap by forming a cable along regenerated axons and can enhance the regeneration of peripheral nerves (Kim et al., 1994), secrete growth factors, and enhance axonal regeneration when transplanted into the injured peripheral nervous system (PNS) (Levi et al., 1994; Maffei et al., 1990). Schwann cells also support regeneration of axons, myelinate axons, reduce cavity formation, reduce secondary damage, and improve hind-limb movement in the injured central nervous system (CNS) (Schaal et al., 2007; Takami et al., 2002; Wiliams and Bunge, 2012). In injured PNS and CNS, it is required to construct substrates that promote axonal growth. Schwann-cell grafts serve as bridges across an axonal gap in the injured CNS and PNS (Richardson et al., 1980; David and Aguayo, 1981; Xu et al., 1997, 1995).

Human Schwann cells are capable of myelinating regenerating rat axons (Baehr and Bunge, 1989). Schwann cells are safe and effective for accelerating the regeneration of transected axons and for the functional recovery of injured nerves (Li and Raisman, 1994). However, it is difficult to obtain and maintain autologous Schwann cells for clinical use. Here we show that OS cells can differentiate into Schwann cells in injured peripheral nerves.

Conclusions

We show that HBCs and OS cells express OPC and astrocyte markers and that OS cells differentiate into oligodendrocytes and Schwann cells. OS cells show promise for treating SCI by recruiting them from autologous olfactory mucosa, thereby eliminating treatment with immunosuppressants. Moreover, olfactory mucosa can be harvested by relatively non-invasive endoscopic surgery. Our future research will focus on assessing the potential of human OS cells for translation to the clinic. It is important to note that human OS cells retain their ability to produce oligodendrocytes and Schwann cells. Further, we will continue investigating the mechanism and the potential of multidisciplinary differentiation for animal OS cells. In conclusion, OS cells are a source of oligodendrocyte and Schwann cell progenitors that show promise for cell-replacement therapies.

Conflict of interest

The authors declare no competing financial interests.

Acknowledgments

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