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**Mini review**

# Adult stem cell transplantation for the treatment of spinal cord injury

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**Abstract**

Cell transplantation has been extensively studied to treat spinal cord injury (SCI). Various kinds of cell have been used as transplants. The most promising transplants are autografts, in which transplantable cells should be derived from adult tissues. In this respect, bone marrow stromal cells (BMSCs), adipose-derived stem cells (ADSCs), and skin-derived stem cells (SDSCs) are appropriate candidates as transplants for SCI. In fact, BMSCs have been extensively studied as a promising transplant for the treatment of SCI. Several studies have been reported concerning the effects of transplanting ADSCs and SDSCs for SCI. On the other hand, embryo-derived or genetically altered cells are associated with marked ethical and tumorigenic concerns. In the present review, we focus on cell transplants that are easily obtainable from adult tissues, and readily applicable for SCI. We think that only those cells that can be used as transplants for clinical cases have a meaning in regenerative medicine.

## Introduction

Generally, peripheral nerve fibers can regenerate very well, whereas central nerve fibers cannot. This difference in the ability to regenerate posed a serious problem regarding the central nervous system (CNS). It had been generally believed that, unlike axonal regeneration in the peripheral nervous system (PNS), neurons in the CNS could not produce axonal sprouts following injury. However, Cajal's study clearly showed that this was not true: CNS axons had the ability to produce regenerating sprouts, which, however, cannot elongate further through a lesion in the CNS (Cajal, 1928). This is the reason why nerve regeneration cannot occur in the CNS. Why are axonal sprouts produced at the injured stumps unable to elongate in the CNS environment? What is the difference in the microenvironment between the PNS and CNS? The major difference in the PNS and CNS may be tissue structures: there are extracellular matrices called endoneurium in the spaces surrounding individual nerve fibers in the PNS, whereas no such distinct extracellular matrix is present in the CNS. Cellular components including myelinated axons are tightly packed without intervening collagen fibril-containing extracellular matrices in the CNS. This might be a major difference contributing to the ability of axons to regenerate following nerve injury in the CNS.

On the other hand, it has been recognized that extracellular matrices serve as a scaffold for the outgrowth of regenerating axons in the PNS: regenerating axons extend through the collagen fibril-containing extracellular matri-

ces as well as along the inner surface of Schwann cell basal laminae (Ide et al., 1983).

Cell therapy for spinal cord injury began with the study of peripheral nerve segment transplantation into the spinal cord and medulla oblongata in the rat (David and Aguayo, 1981). Neurons located within the spinal cord and medulla oblongata emanated regenerating axons and extended over a long distance through the implanted peripheral nerve segments. This study clearly demonstrated that axons of the CNS can regenerate in an appropriate environment just as in peripheral nerve segments.

Various kinds of cell have so far been used as transplants for cell therapy in spinal cord injury, including Schwann cells (Xu et al., 1999; Golden et al., 2007; Someya et al., 2008), cultured cerebellar neurons (Shimizu, 1983), embryonic spinal cord tissue (Iwashita et al., 1994), olfactory ensheathing cells (Li et al., 1997; Ramon-Cueto, 2000; Plant et al., 2003), macrophages (Rapalino et al., 1998; Knoller et al., 2005), choroid plexus epithelial cells (Ide et al., 2001; Matsumoto et al., 2003), ES cells (McDonald et al., 1999), and bone marrow stromal cells (Wu et al., 2003; Hofstetter et al., 2002; Ohta et al., 2004; Himes et al., 2006, Lu et al., 2007).

As Schwann cells play a major role in axonal regeneration in the PNS, it is reasonable to use Schwann cells as transplants for axonal regeneration in spinal cord injury (SCI). In fact, implanted Schwann cells facilitated axonal regeneration in SCI. However, the problem was that regenerated axons could not extend further into the host spinal cord tissue: regenerating axons could not extend beyond the lesion into the host spinal cord. This means that regenerating axons might not form a neural connection with the host nervous system, suggesting an absence of a contribution to functional improvement. Various techniques have been studied to make regenerating axons extend further beyond the border of the lesion; however, there is no effective way to overcome this problem.

Cultured neurons had been studied as transplants for SCI before the advent of the current large-scale cell therapy for SCI. The classical transplantation study of cultured neurons was performed about 30 years ago by Shimizu and colleagues (Shimizu, 1983), who transplanted cultured cerebellar neurons into spinal cord lesions of dogs. They assessed the effects of cell transplantation by observing the locomotory behaviors of the dogs as well as histological findings of spinal cord lesions. The basic concept of their study was the same as that of the current cell transplantation study.

Olfactory ensheathing cells (OECs) have been extensively studied. They are already used for clinical cases in some countries (Lima et al., 2006). OECs surround olfactory nerve axons, as in the case of Schwann cells in the PNS. Olfactory neurons characteristically retain the ability to regenerate, even in adults. Newly produced neurons emanate regenerating axons that can extend through the scaffolds of OECs into the olfactory bulb. This means that OECs provide suitable pathways for regenerating axons to extend from the PNS to CNS environments, indicating that OECs have the dual functions of Schwann cells and astrocytes. Owing to this characteristic dual property, OECs are believed to support the growth of regenerating axons in the SCI. OECs have already been applied to clinical cases in some countries; however, the clinical outcomes have not been sufficiently evaluated to verify the hypothesis that olfactory ensheathing cells are in fact involved in the facilitation of regenerating axon growth in SCI.

Choroid plexus epithelial cells are a continuation of ventricular ependymal cells. The grafting of choroid plexus tissue segments induced vigorous axonal outgrowth within the spinal cord lesion. This suggests that choroid plexus epithelial cells (CPECs) might be used as transplants for the treatment of SCI. It should be noted that CPECs are a type of glial cell. Our previous study demonstrated that neural stem cells can be produced from CPECs in vitro (Itokazu et al., 2006). This means that CPECs might be a rare neural tissue from which adult neural stem cells can be produced, that are available for cell therapy in SCI.

The role of macrophages in spinal cord regeneration has been extensively studied from immunological perspectives by an Israeli group. The concept of their study was to utilize immunological reactions in SCI; they studied transplantation of activated macrophages. The clinical application of macrophages to SCI was planned, but no report on the outcomes of clinical cases has been published.

Embryonal tissues and ES cells involve se-

rious ethical problems regarding clinical application. Even if the transplantation of these cells has had some beneficial effects on SCI in experimental animals, their clinical application has been prohibited due to the associated serious ethical problem. Considering that the final goal of stem cell research for cell therapy is to apply research achievements for the treatment of diseases, cells that cannot be clinically applied are useless and have no significance in regenerative medicine. Although many studies have been conducted, ES cells have not yet been applied to clinical cases.

On the other hand, iPS cells have been received with considerable interest as a dream stem cell free from ethical problems. iPS cells have been paid much attention as a promising type of stem cell for regenerative medicine including SCI treatment. However, there has been no scientific report so far on the use of iPS cells as transplants for SCI. There are many problems concerning iPS cells used as transplants for SCI. One of the problems is the tumorigenic property of iPS cells. Undifferentiated iPS cells should not be present in the transplants. Any trace of undifferentiated cells in the transplants might cause tumor development in the host. This means that iPS cells should be completely differentiated before transplantation. For this purpose, an effective method should be established to fully differentiate iPS cells into neurons or glial cells. Another problem is that it is not known whether iPS-differentiated neurons can survive and truly promote axonal regeneration after transplantation in spinal cord lesions. No report is available concerning whether iPS-differentiated neurons or glial cells are efficient transplants in SCI. iPS cells are not natural cells, but are forcefully changed into undifferentiated cells, which may cause some unexpected adverse reactions disturbing the normal tissue functions in vivo. These disadvantages regarding clinical application lessen the value of iPS cells. It is critically important for stem cells in regenerative medicine to be able to be used for clinical cell therapy. The question of whether iPS cells could have real benefits in regenerative medicine should be addressed. Stem cells for regenerative medicine should be safe and demonstrated to have beneficial effects in cell therapy. In this respect, stem cells derived from adult tissues are most desirable as transplants: they are normal cells residing in adult tissues, and safe for use as autologous transplants.

Recently, adult stem cells have been studied extensively. Adult stem cells include BMSCs, ADSCs, and EDSCs. They are available from adult tissues, and can be used as autologous transplants for cell therapy. These tissues are easily obtainable, and have none of the ethical problems seen with ES or iPS cells, suggesting that they are readily available for use in clinical cell therapy. All of these three types of stem cell are derived from non-nervous tissues. Nevertheless, they have been studied as transplants in SCI. BMSCs have been studied most extensively, and shown to have beneficial effects on spinal cord regeneration.

In the present mini-review, we would like to survey the recent trends in cell therapy using these adult stem cells in SCI.

**Bone marrow stromal cells (BMSCs)**

We have been involved for several years in the study of BMSCs for SCI treatment. BMSCs are cultured from the bone marrow of adult rats, and are considered to contain a small population of stem cells.

We showed that BMSC transplantation immediately after SCI reduced cavity formation and enhanced axonal outgrowth in the SCI lesion (Wu et al., 2003). Electron microscopy showed that transplanted BMSCs are located in the lesion, in which the extensive outgrowth of immature axons occurred in the extracellular matrices.

Next, we studied cell infusion through the cerebro-spinal fluid (CSF) in acute SCI. BMSCs were injected into the $4^{th}$ ventricle. Injected BMSCs were transported by the flow of CSF to the spinal cord, and a few of them invaded the lesion, while many became attached to the surface of the spinal cord. In this experiment, the locomotory function improved, cavity formation was reduced, and host axons around the lesion were rescued from degeneration (Ohta et al., 2004). Based on the fact that, although only a few of them invaded the lesion, BMSCs promoted the repair of the injured spinal cord, it was suggested that BMSCs might secrete some effective substances, which can be transported through the CSF to the lesion. Such substances might function to rescue affected axons from degeneration, and facilitate axonal regeneration in the SCI. Based on this study, and verifying the safety of injecting BMSCs

into CSF of a monkey, we proceeded to the clinical application of BMSC injection through the CSF in a patient with acute SCI (Saito et al., 2008). Five patients have so far been treated by BMSC injection into the CSF via lumbar puncture. Mononuclear cells derived from the bone marrow have almost the same effects on SCI as BMSCs (Yoshihara et al., 2007).

Recently, we studied the effect of BMSC transplantation on subacute SCI (Ide et al., 2010). Rats were crush-injured at the Th 8–9 level by dropping a 10-g metal rod onto the exposed spinal cord. Two weeks later, BMSCs were transplanted by injecting them directly into the lesion. It was shown that, even if BMSCs disappeared from the spinal cord, there was extensive axonal outgrowth through the extracellular matrices within the spinal cord. Cavity formation was markedly reduced, and the locomotory behavior improved. This showed that BMSC transplantation might be effective even for subacute SCI.

This study showed that there was an extensive induction of extracellular matrices in the spinal cord lesion. Axonal outgrowth occurred through such extracellular matrices. Regenerating axons are immature, and surrounded by developing Schwann cells (Fig. 1). These

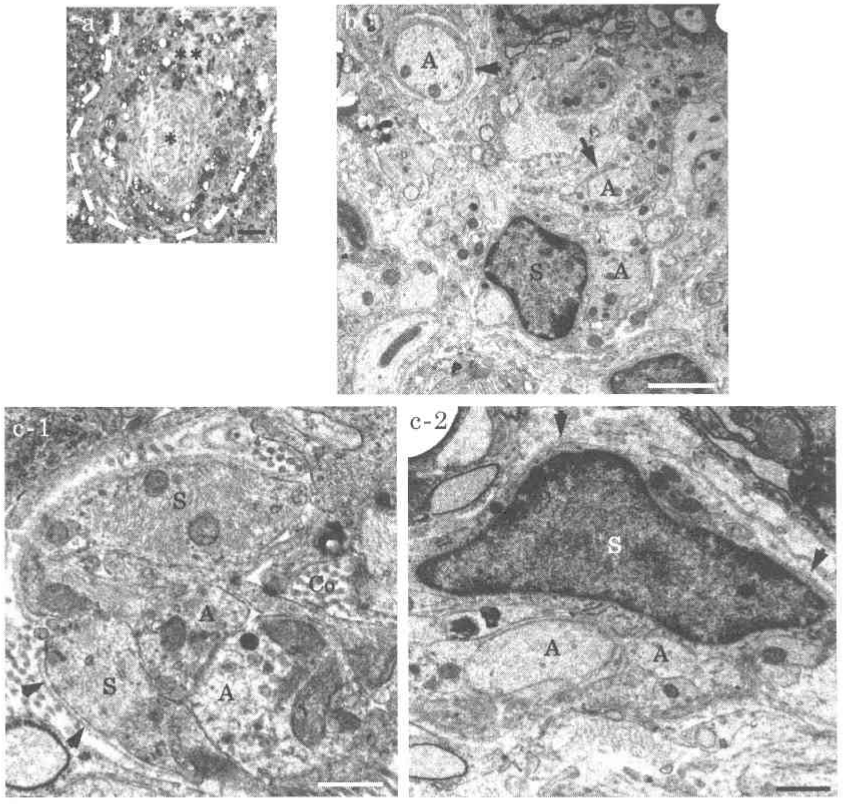


Fig. 1 Electron microscopy. One week after transplantation

a. Epon section. A cell assembly (asterisk) presumed to be engrafted BMSCs is located in the dorsal part of the spinal cord. The border of host white matter is marked by a dotted line. Scale: 50 $\mu$m

b. Electron micrograph taken from the area dorsal to the cell assembly in "a". There are numerous unmyelinated immature axons (some are labeled "A") covered by cell processes (arrows) or a cell body (S), suggesting that these axon-associated cells might be developing Schwann cells. These unmyelinated immature axons are considered to be regenerating axons, but not remaining host axons. Scale: 2$\mu$m

c-1. Magnification of an axon bundle. Two axons (A) are surrounded by cell processes (S) of developing Schwann cells with basal laminae (arrows) on their surface. There are collagen fibrils (Co) around the nerve bundle. Scale: 500 nm

c-2. A developing Schwann cell (S) covered by basal lamina (arrows) surrounds unmyelinated immature axons (A). Scale: 1 $\mu$m

(Reproduction from Ide et al., Brain Res., 2010)

regenerating axons gradually developed to form myelin sheaths beyond 2 weeks post-transplantation (Fig. 2). These features are similar to those seen in peripheral nerve regeneration. It was unexpected that the peripheral nerve environment is formed within the spinal cord, through which nerve regeneration occurs. BMSCs might be involved in the induction of extracellular matrices, which form effective scaffolds for axonal outgrowth. In addition, it is probable that BMSCs secrete, as described above, some effective molecules to promote axonal survival and regeneration.

Numerous Schwann cells surrounded regenerating axons. The source of these Schwann cells was unknown. One possibility was the dorsal roots located near the lesion. In this experiment, it might be less probable that regenerating axons came from the roots, because regenerating axons appeared to be continuous with the nerve fibers within the spinal cord. Schwann cells from the roots might migrate to the regenerating axons in the spinal cord. Another possibility is that there might be some Schwann cell sources within the spinal cord, but this remains to be demonstrated. The third possibility is the transdifferentiation of BMSCs into Schwann cells within the spinal cord. This might be rather unlikely because no Schwann cells were labeled by GFP, the cell marker for engrafted BMSCs.

The involvement of Schwann cells in axonal outgrowth within the spinal cord has been reported in several studies (Lu et al., 2007; Ankeny et al., 2004; Himes et al., 2006; Hofstetter et al., 2002). In addition, Lu et al. (2007) indicated the induction of extracellular matrices by showing the presence of NG2, L1, and laminin employing immunohistochemistry: NG2 might be related to proteoglycans of extracellular matrices, L1 might be expressed on the contact of axons with Schwann cells, and laminin might be derived from the basal laminae on the surface of Schwann cells associated with axons.

Cavity formation was markedly reduced (Fig. 2). The spinal cord lesion was mostly filled with the proliferated extracellular matrices in the cell-transplanted rats. On the contrary, large cavities were formed in the lesion of the control.

The BBB score for the locomotory function was assessed by observing the behaviors of rats for 5 min in the open field. The behaviors were recorded by video camera, and evaluated by 2 persons blinded to the experiment. BBB scores were about 9–10 in the transplantation group, while 5–6 in the control (Fig. 3). The difference of 4–5 points is marked.

The tissue condition of the spinal cord lesion might be markedly different between acute and chronic SCI. Cell transplantation in acute SCI can be performed experimentally, but is not practical in clinical cases. There might be glial scar formation around the cavity in chronic SCI. We thought that a subacute or chronic lesion in SCI might become separated by a glial scar from the CSF, suggesting that cells infused into the CSF may not be able to access the lesion. Therefore, we engrafted BMSCs directly into the lesion in this subacute SCI model.

Crush injury reflects the contusion injury of clinical SCI. Therefore, we usually employ crush injury in experiments. Transection injury cuts open the pia mater, leading to the exposure of spinal cord tissue to the surrounding extra-spinal cord tissues, resulting in infiltration of connective tissues into the spinal cord.

Our previous study indicated that trophic factors might play a major role in the repair of spinal cord injury. The trophic factors were considered to contribute to the survival of degenerating axons and the outgrowth of regenerating axons, as noted above. Several other studies suggested that BMSCs release diffusible neuroprotective factors (Chopp et al., 2000; Ankeny et al., 2004; Swanger et al., 2005; Himes et al., 2006; Shintani et al., 2007). It has been shown that BMSCs release trophic factors including BDNF, VEGF, and cytokines such as IL-6 and stem cell factor (Neuhuber et al., 2005), and IGF-1 (Ohtaki et al., 2008). We examined the effect of conditioned medium (CM) of BMSC culture. The CM has a potent effect on neuronal survival and neurite extension. Biochemical analysis revealed that the CM contains various trophic factors including those above-mentioned. However, bioassay analysis showed that individual factors or their combinations did not have the same effects as the CM on neuronal survival and neurite extension.

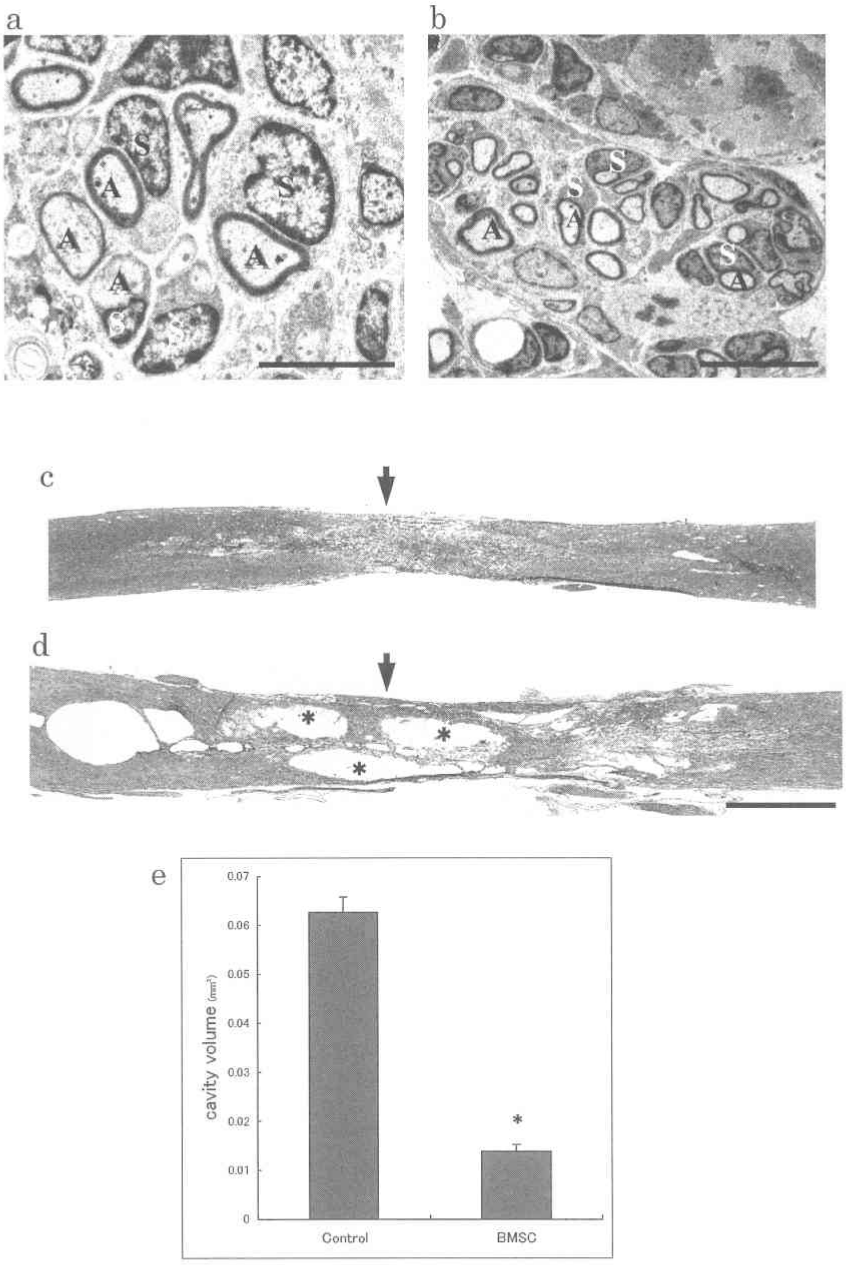


Fig. 2 Electron microscopy of axons extending through the lesion at 2 and 8 weeks (a and b), and reduction in cavity formation at 8 weeks after BMSC transplantation (c, d and e)

a. Two weeks after transplantation. Individual axons (A) are covered by Schwann cells (S). Some are myelinated. Scale: 5 $\mu$m

b. Eight weeks after transplantation. Individual axons (A) are thickly myelinated by Schwann cells (S). Scale: 10 $\mu$m

c. Horizontal section of the spinal cord following BMSC transplantation. The lesion (arrow) is filled with tissues. HE staining.

d. Control. Vehicle injection. Cavities (asterisks) are formed in the lesion (arrow). HE staining. Scale: 2 mm (c and d)

e. This graph shows a comparison of the volume of the spinal cord cavity between control and BMSC transplantation groups. The difference is significant (asterisk, $P < 0.01$).

(Reproduction from Ide et al., Brain Res., 2010)

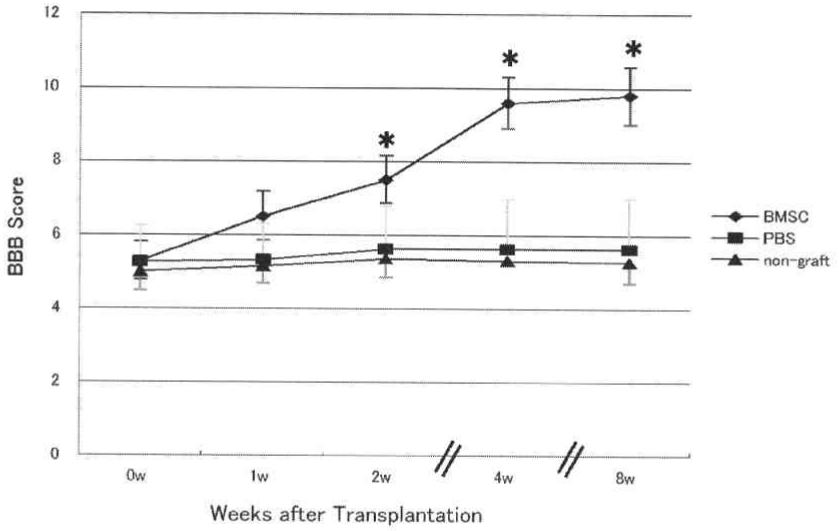


Fig. 3 Locomotory behavior
This graph shows BBB scores in rats of cell transplantation and control groups 10weeks after injury (8 weeks after cell transplantation). There are significant differences ($P<0.05$) between cell transplantation and control groups 2, 4, and 8 weeks after BMSC transplantation (asterisks). (Reproduction from Ide et al., Brain Res., 2010)

**Adipose-derived stem cells (ADSCs)**

Adipose tissue is mesenchymal, distributing as a component of connective tissues. It has recently been demonstrated that adipose tissue contains stem cells which can transdifferentiate into osteocytes, chondrocytes, and even neural cells including neurons and glial cells in vitro (Safford et al., 2002, 2004). Safford et al. (2002) cultured ADSCs in medium containing butylated hydiroxyanisole, valproic acid, forskolin, hydrocortisone, and insulin, and observed the differentiation of ADSCs into cells with a neuron-like morphology. They presented data from immunohistochemistry and immunobotting, showing that the neuron-like cells expressed neuronal markers including MAP (myelin associate protein), GFAP, and GAP-43 (growthassociated protein). However, it was suggested that ADSCs changed into neuron-like cells due to cellular damage in medium containing several unusual factors for cell differentiation.

Huang et al. (2007) studied the differentiation of stem cells obtained from the adipose tissues of facial and abdominal subcutaneous regions. ADSCs are positive for CD29, CD44, and CD 90. They described that ADSCs were differentiated into osteocytes, chondrocytes, and neurons in vitro. They presented data on immunohistochemistry and immunobotting, as in the paper of Safford et al. (2002, 2004).

Although it is generally accepted that ADSCs differentiate into osteocytes and chondrocytes, whether ADSCs differentiate into neurons is controversial. Transdifferentiated neurons should be identified not only based on morphological and immunohistochemical data, but also by electrophysiological characteristics.

An early transplantation study of ADSCs showed effective results regarding spinal cord regeneration (Kang et al., 2006).

Tapp et al. (2009) highly evaluated adult tissue-derived stem cells including BMSCs, ADSCs, and SDSCs which were easily available, and used clinically in regenerative medicine. They studied the differentiation of stem cells from adipose tissues of the facial and abdominal subcutaneous regions. Various surface antigens have been used for the characterization of these mesenchymal stem cells: CD73 (surface enzyme), CD90 and CD105 (both are extracellular matrix protein), And CD 29 (integrin). On the other hand, hematopoietic markers such as CD45, CD34, CD14, CD 11b, and CD19 are not present on mesenchymal stem cells. They used scaffolds such as collagen fibrils, chitosan, gelatin, chondroitin sulfate, and alginate for the differentiation of ADSCs into osteocytes, and chondrocytes. No clear marker criteria to

differentiate between ADCs, BMSCs, and fibroblasts are currently available.

Rhu et al. (2009) performed the allogeneic transplantation of ADSCs derived from adult dogs into SCI produced by epidural balloon compression 1 week before transplantation. ADSCs were positive for CD 44, 90, and 105, but negative for CD 14, 34, and 45.

Five to nine weeks after transplantation, dogs showed an improved locomotory function. Cavity formation was reduced, and extensive axonal growth occurred in the lesion. They indicated that ADSCs might be transdiffferentiated into astrocytes, neurons, and oligodendrocytes. MRI pictures and corresponding HE sections were shown in parallel, indicating that T2-wighted MRI reflects the CSF in the subarachnoidal space and cavities. This study did not clearly describe how transplanted ASDCs contributed to axonal outgrowth and caused functional recovery.

Zhang et al. (2009) obtained neurospheres from subventricular CNS tissue and even from non-nervous tissues including ADSCs and BMSCs by culturing in medium containing EGF (epidermal growth factor) and bFGF (basic fibroblast growth factor) for 5-7 days. They were transdifferentiated into neurons, astrocytes, and oligodendrocytes. Astrocytes were the most abundant, followed by neurons and oligodendrocytes. These neurospheres were implanted directly into the lesion 1 week after SCI. Locomotory functions were improved, and cavity formation was reduced, with the highest effectiveness shown by neurospheres from the subventricular zone, followed by BMSCs and ADSCs. They used BrdU for cell labeling, which could label host cells, leading to the misinterpretation of the fate of transplanted cells in vivo. How axonal outgrowth occurred in the lesion and how regenerated axons interacted with the host neural networks were not clarified in this study.

The transdifferentiation of engrafted cells might not be a major problem. The most important question is how cell transplantation induces axons to regenerate in the lesion, and extend further into the host tissue to form efficient connections with the host neural networks in SCI. No study has focused on this.

**Skin-derived stem cells (SDSCs)**

The skin consists of two components, the epidermis and dermis. The cells in the epidermal basal layer continue to be proliferative even in adults. In addition, hair follicles contain proliferative cells which contribute to the hair cycle and to epidermal regeneration as a source of stem cells in the severe skin lesions. It has been demonstrated that SDSCs come almost exclusively from hair follicles including the bulge located near the sebaceous gland and dermal papilla at the bottom. It should be noted that these stem cells can be regarded as a lineage of neural crest cells.

Multipotent neural crest cells have been identified at other sites including the spinal and sympathetic ganglia (Duff et al., 1991), and the gastrointestinal tract (Kruger et al., 2002).

Hoffman (2006) described the hair follicle bulge as an abundant, easily accessible source of actively growing pluripotent adult stem cells, expressing nestin, that differentiate into neurons, glial cells, keratinocytes, and smooth muscle cells in vitro. In his experiment, hair follicle stem cells that had been implanted into the gap regions of a severed sciatic nerve transdifferentiated into Schwann cells, which markedly enhanced the rate of nerve regeneration and restoration of nerve functions.

Yu et al. (2006) demonstrated multipotent stem cells in hair follicles including the bulge, using the medium for the culture of human ES cells. These cells express ES cell markers including Nanog and Oct4, as well as neural crest cell markers.

They obtained cell spheres from hair follicles, and cultured them attached to the culture dish, from which melanocytes, neurons, and smooth muscle cells were differentiated in the differentiation medium specific for each cell type.

Sieber-Blum et al. (2004, 2006) explanted bulges from adult mouse whisker follicles to produce clonal cells, including neurons, smooth muscle cells, Schwann cells, and melanocytes. SDSCs differentiated into Schwann cells due to the presence of neuregulin-1, and into chondrocytes due to bone morphogenetic protein-2. They concluded that epidermal neural crest cells are promising candidates for diverse cell therapy paradigms because of their high degree of inherent plasticity and due to their easy accessibility in the skin.

Hunt et al. (2008) described the hair follicle dermal papilla as a niche of precursor cells with neuronal and glial potential. They used the Wnt-1-cre/R26R mouse, in which neural crest cells can be identified by immunohistochemistry for β-galactosidase. Neural crest cells expressed Pax3 and slug. Cell spheres obtained from dermal papillae were cultured in medium containing BDNF, BGF, NT-3, retinoic acid, and FGF-2 to induce differentiation into neuronal cells. For Schwann cell differentiation, cell spheres were cultured in medium containing neuregulin and forskolin. They demonstrated that neuronal and glial cells were also produced from human hair follicles in the facial skin.

Sieber-Blum and Hu (2008) described in their review article that epidermal neural crest cells (i. e., SDSCs) have the genes c-Myc, Klf4, Sox2, and Lin28, similar to those in iPS cells. Oct4 and Nanog are present at very low levels in epidermal stem cells. These two genes are considered to be responsible for the tumorigenic property of these cells following transplantation. They emphasized that the low content of these genes indicated the low tumorigenic potential of neural crest stem cells.

Hu et al. (2006) demonstrated the molecular characteristics of epidermal neural crest stem cells by identifying 19 genes representative of epidermal neural crest stem cells.

Wong et al. (2006) showed that SDSCs from face whisker follicles had asphere-forming potential and exhibited multipotential properties, while those from hair follicles in the trunk skin were restricted to the glial and melanocyte lineages. Sphere-forming SDSCs from adult mouse skin displayed a rather restricted potential in vivo. SDSC spheres, when dissociated and injected into the lateral ventricles of rat and chicken embryos, remained largely undifferentiated as cell aggregates close to the injection site, and failed to integrate into the host central nervous system tissue. This is in contrast to neural progenitors obtained from ES cells or neural stem cells from the CNS. The authors did not observe neural differentiation, tissue integration, or behavioral improvement upon the transplantation of SDSCs into the striatum of a 6-hydroxydopamine-lesioned mouse model for Parkinson disease, or on intravenous injection into mice with experimental autoimmune encephalomyelitis. These trials suggest that SDSCs from adult skin, when transplanted into the CNS, cannot transdifferentiate into neural cell types in the CNS.

Biernaskie et al. (2007) used murine SDSCs for transplantation. SDSCs were differentiated into Schwann cells (SDSC-SC) before transplantation. In addition, they prepared neural stem cells (NS) derived from the forebrain subventricular zone. They compared the effects of SDSC-SC, SDSCs, and NS on spinal cord regeneration by transplanting them into a rat spinal cord lesion. SDSC-SC and SDSCs promoted the recruitment of endogenous Schwann cells into the lesion. They showed that SDSC-SC transplantation was the most effective for axonal regeneration, cavity reduction, and improvement of the locomotory function. They also indicated the changes in extracellular matrices by immunohistochemistry for neurocan and laminin. Axonal outgrowth was shown by immunohistochemistry for serotonin (5HT), calcitonin gene-related protein (CGRP), and tyrosine hydroxylase (TH). There is no clear description concerning how axonal regeneration was facilitated by cell transplantation. Their study suggests that regenerating axons surrounded by both endo- and exogenous Schwann cells grew through extracellular matrices; however, there is no statement regarding this consideration. It is interesting to compare the effects of NS with those of SDSC-SC and SDSCs involving a comparison between neuronal and non-neuronal cells. However, no description concerning the comparison of these cells was given in their study.

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