Treatment of spinal cord injury by transplantation of cells via cerebrospinal fluid

Yan LIU¹, Hong-Yun HUANG^{1,2,3}

¹*Division of Spinal Cord Injury, Beijing Hongtianji Neuroscience Academy, Beijing 100144, China*

²*Department of Neurosurgery, Beijing Rehabilitation Center, Beijing 100144, China*

³*Neuroscience Institute of Taishan Medical University, Beijing 100144, China*

Abstract: It is very important to probe into the axonal regeneration and functional recovery of central nervous system (CNS) after implantation of cells into cerebrospinal fluid (CSF) for spinal cord injury (SCI). Transplantation of cells via CSF poses great potentials for SCI in clinic. Studies on administration of cells via CSF indicate that the method is safe and convenient. The method is more suitable to treating multiple lesions of the CNS since it does not produce open lesions. However, there are disputes over its promotion effects on axonal regeneration and functional recovery of spinal cord after injury; and some questions, such as the mechanisms of functional recovery of spinal cord, the proper time window of cell transplantation, and cell types of transplantation, still need to be handled. This review summarized the method of cell transplantation via CSF for treatment of SCI.

Keywords: cell transplantation; cerebrospinal fluid; subarachnoid space

1 Introduction

Besides production of CSF, choroid plexus has several other functions. It produces and secretes an impressive array of growth factors, neurotrophins^[1], and a number of enzymes that degrade and eliminate potentially toxic molecules^[2,3]. Furthermore, the rates of CSF production and CSF flow are strongly associated with the health of CNS^[4,5]. Normal CSF works as a trophic factor for fetal primary cell culture^[6], whereas in some pathological conditions such as Parkinson's disease^[7] and multiple sclerosis^[8], it caused apoptosis of cultured neural cells. Intracerebroventricular injection has been widely used to administer peptides^[9], drugs^[10], neurotrophic factors^[11], and cells^[12] into the brain or spinal cord for various purposes.

Cerebral cortex and subarachnoid space, both of which are immunological privileged sites, provide best protection for allograft. In 1984, dispersed single pancreatic endocrine cells (PECs) were imbedded into the subarachnoid space by Tze *et al.*^[13] and survived. These dispersed single PEC could be transplanted as a permanent functional graft and could normalize the hyperglycemia of diabetic recipients^[13-15]. It was reported that the cisterna magna could serve as an immunological privileged site for the implanted allogeneic pancreatic islets, and the islets in CSF could regulate and maintain normal glucose homeostasis via secretion of insulin across the blood-brain barrier^[16]. However, although the blood-brain barrier and blood cerebrospinal fluid barrier can maintain the CNS as an immunological privileged site, T lymphocytes can migrate through the unstimulated brain endothelium and epithelium to perform immune surveillance or initiate inflammation^[17]. Therefore, the immunological protection offered to allogeneic transplants by the CNS is incomplete.

Cell transplantation is a hot issue in treating CNS diseases, but transplanting the cells into the parenchyma of

Corresponding author: Hong-Yun HUANG
Tel: 86-10-51625668
Fax: 86-10-51625990
E-mail: hongyunh@gmail.com
Article ID: 1673-7067(2008)-05-0323-06
CLC number: Q42
Document code: A
Received date: 2008-06-18

CNS may make impairment to the patients, since the skull or vertebral plate must be opened during the transplantation process. On the contrary, transplantation of cells via CSF is safe, convenient and without any open lesion. Here we would summarize the feasibility, safety and effectiveness of cell transplantation via CSF for treatment of SCI.

2 Transplantation of cells via CSF for treatment of neuropathic pain

Neuropathic pain is a major health problem. About 95% SCI patients have neuropathic pain problems. Neuropathic pain is defined as a kind of pain initiated or caused by a primary lesion or dysfunction in the nervous system^[18]. Neuropathic pain has a variety of clinical symptoms. It often has a continuous burning character and accompanies with the presence of abnormal sensory symptoms, such as hyperalgesia and allodynia^[19]. Chronic pain can cause depression, decrease quality of life, and is difficult to manage. Pharmacological treatment for the symptoms of painful neuropathy is difficult, because the mechanism is poorly understood, and an effective dose of analgesic can also produce multiple side effects^[20]. Cell therapy is considered as a hopeful method for neuropathic pain following the SCI, although it is in the infancy stage. The cellular strategies, which would replace or assist the existed pharmacological treatment of neuropathic pain, have progressed tremendously over the past 20 years.

Some cell lines can play roles as biologic “minipumps” to deliver anti-nociceptive molecules near the pain processing centers of the spinal cord after nerve injury, which is a newly developing technology for treatment of neuropathic pain.

The earliest cells used for pain relief were adrenal chromaffin cells from rat or bovine, which were placed in the subarachnoid space near the spinal cord pain-processing pathways. Functioned as cellular minipumps, these grafts secreted a cocktail of anti-nociceptive agents around the spinal cord for alleviating peripheral nerve injury, inflammatory or arthritic pain. Immunoprotected allogeneic or xenogeneic chromaffin cells could act as “minipumps” to continuously deliver neuroactive substances, and could be used for treatment of patients suffered from neuropathic pain^[21]. Bovine chromaffin cells and porcine chromaffin cells, when spinally transplanted into the subarachnoid space of rats as xenografts, can produce antinociception^[22]. Chitosan-based

matrices, as the cell substrates for bovine chromaffin cell attachment in transplantation procedures, were found more readily to attach chromaffin cells; and the chromaffin cells can survive for at least two weeks *in vitro* or after subarachnoid grafting to rats^[23]. These findings suggest that the intrathecal microencapsulation of chromaffin cells might be a useful method for treating chronic pain^[24]. Also, transplantation of adrenal medullary chromaffin cells into the spinal subarachnoid space has been shown to decrease pain responses in the formalin model of neurogenic inflammatory pain and the chronic constriction injury (CCI) model^[25], as an encapsulating membrane can provide an immunological privileged site enabling successful xenogeneic transplantation^[26,27]. This suggests that transplanting functional encapsulated xenogeneic chromaffin cells into the CSF should be useful for human clinical trials in the patients suffered from refractory terminal cancer pain.

The bioengineered cells, such as the AtT-20 cells, the cells transfected with human proenkephalin gene, the cells secreting enkephalin or β -endorphin, the catecholamine-releasing cells, and B16F1C29 melanoma cells, are also the candidate cells for treatment of neuralgia. These cells may provide an choice for treatment of chronic intractable pain^[28-30]. For example, after transplantation into the subarachnoid space of the lumbar spinal cord, the bioengineered serotonergic cells can survive longer than 7 weeks. These transplanted cells can synthesize 5-hydroxytryptamine (5-HT) and brain-derived neurotrophic factor (BDNF), and thus ameliorate or reverse chronic pain. Using the neural cell lines that have been genetically modified to capable to deliver the anti-nociceptive molecules, such as galanin and γ -aminobutyric acid (GABA), as the transplants offers a safe and novel approach to manage the CCI-initiated pain^[31-33]. Such “biologic minipumps” can be developed for safe use in humans. The alteration of spinal GABA level may contribute to the early development of chronic neuropathic pain, which could be prevented by early intervention with cellular therapy to restore the GABA level^[34]. The polymer-encapsulated mouse neuroblastoma cells capable of secreting β -endorphin can reduce pain sensitivity, and the encapsulated cell technology is discussed with an emphasis on developing pain-modulating clinical devices in recent years^[35].

According to the update research, subarachnoid transplantation of a human neuronal cell line with a spinal tap can

attenuates chronic allodynia and hyperalgesia after excitotoxic spinal cord injury in rat. These human cells could affect the intrathecal spinal environment for sensory system modulation^[36]. In addition, after transplantation of the immortalized astrocyte line carrying the human preproenkephalin gene (IASL/hPPE) into the subarachnoid space of CCI rats, the cells were able to reverse the development of chronic neuropathic pain during 2–7 weeks after grafts^[37].

It is important that the transplanted cell, as a therapeutic agent, should be reproducible, safe, and controllable. However, there are no a homogeneous, expandable cell source to supply the anti-nociceptive agents. Although these cell lines are at the early stage of investigation, their clinical anti-nociceptive potential is significant for treating the neuropathic pain of SCI^[37,38].

3 Transplantation of cells via CSF for CNS regeneration

Disorders of the central nervous system are a major concern in modern human society. Over the past two decades, it has become increasingly clear that the adult brain and spinal cord are responsive to the signals of several classes of molecules that can promote neuronal survival and stimulate axon outgrowth. Numerous studies have indicated that cell transplantation can promote neuronal repair^[39]. Transplantation of neural stem cells has been well studied recently, and it is considered as a very hopeful approach for treatment of CNS diseases^[40–42]. Cells were generally transplanted by direct injection into the brain^[43,44] or injured spinal cord^[45,46]. However, direct injection of cells into the lesion sites is unrealistic in clinic when the lesion is widely spread or multifocal. In recent years, transplantation of cell via CSF attracts more attention in treating multifocal lesions. Some studies found that those neural stem cells administered into the ventricles of the fetal brain may differentiate and migrate during fetal development^[47,48]. Another study found that when embryonic neuroepithelial cells were transplanted to the lateral ventricle of rats, the grafts were survived and attached to the ventricle by day 10. Some grafts could migrate into the third ventricle and grew into a mass of cells, as the neuroepithelial cells dissociated from neural tube could survive and differentiate into neurons and astrocytes^[49]. When neurosphere cells were transplanted to the injured spinal cord through the fourth ventricle or cisterna magna, the injected cells were

extensively transported by CSF within the subarachnoid space, and survived as clusters on the pial surface of the spinal cord. Most importantly, these cells can migrate into the lesion sites and integrate into the injured spinal cord tissues^[50–52]. Other studies also found that inflammatory process could attract targeted migration of transplanted precursor cells into the brain parenchyma^[53]. Moreover, the neural stem cells infused through the fourth ventricle might have a beneficial effect on nerve regeneration to enhance axonal growth in injured dorsal roots^[38]. Transplantation of cells into injured spinal cord through ventricle is a unique method to disseminate cells all over the spinal cord, and these cells can migrate and be integrated into the injured spinal cord^[54]. However, little study has been performed on administration of neural stem cells through the CSF to promote the functional recovery of injured spinal cord.

While injected into the rat's subarachnoid space of contusive model of SCI 7 d after injury, Schwann cells demonstrated their presence within spinal cord in the tracing group in 7 d after transplantation. The 60-day post-injury evaluation for rats showed a significant improvement in locomotor performance, and the axon density at the injury site was significantly higher^[55].

The human leptomenigeal cells could be survived after they were transplanted into the C3-dorsal column transection, and positive for the human specific histocompatibility complex, HLA-DR^[56]. The amount of marrow stroma cells (MSCs) observed at the injury site was significantly higher than that in intact spinal cord, and the MSCs infiltrated into the deeper spinal cord parenchyma by the perivascular spaces. Some MSCs could differentiate into the Nestin-positive, immature neurons or glial cells^[57,58]. In our previous research, we also found an interesting phenomenon that the transplanted cells infiltrated into the deeper spinal cord parenchyma by the perivascular spaces, which suggested that, the angiogenesis after injury might be beneficial for the infiltration of transplanted cells. In the rats received transplantation of bone MSCs via CSF, the Basso, Beattie, and Bresnahan (BBB) scoring was higher than that in control rats. However, the grafted cells gradually decreased in number and disappeared within 3 weeks^[39].

The probable explanations for cell immigration and survival in injury site are as follows: (1) The pia mater at the lesion site may provide a suitable substrate for cell

attachment; (2) the pial basal lamina may have been affected by the contusion, allowing cells to invade the injured tissue; and (3) it is also possible that some signals released from injured spinal cord tissues make them attach to the lesion-affected pia mater. As described above, the cells transplanted via CSF can be survival and functional without obvious harmful effect at the injection site. This method can be useful for transplantation of cells and offers hope for the patients suffered from spinal cord injuries. After the cell suspension consisting of cells derived from immature nervous and the hemopoietic tissues were injected into the recipient subarachnoid space through a cerebrospinal puncture for patients in comatose state, the mortality was lower and the quality of life 1.5-year follow-up demonstrated significantly better in comparison with patients of the control group^[59]. Treatment of chronic SCI by transplantation of MSCs into subarachnoid space is effective and safe in short term, but the long-term curative effect needs more observations^[60]. The clinical trial of transplanting MSCs into the CSF has been used in Japanese for treatment of the subacute stage SCI, and the safety of this therapy is confirmed. Although definite improvement in the score of ASIA scale is obtained, the efficacy of this kind of cell transplantation should be evaluated by a committee with members outside this study team after a series of cases in accordance with the protocol^[61,62,39].

As inflammatory process may attract targeted migration of transplanted cells into the parenchyma, and above-mentioned data were come from cell transplantation during acute and subacute phase of injury, the critical issue is the time window of cell transplantation. It needs further exploration on the mechanism of cell transplantation via CSF for treatment of advanced or chronic SCI. It is also the next research direction to choose proper types of cells that can permeate the spinal meninges and migrate into parenchyma of injured spinal cord.

Reference:

- [1] Chodobski A, Szmydynger-Chodobska J. Choroid plexus: target for polypeptides and site of their synthesis. *Microsc Res Tech* 2001, 52: 65-82.
- [2] Gherzi-Egea JF, Strazielle N. Brain drug delivery, drug metabolism, and multidrug resistance at the choroids plexus. *Microsc Res Tech* 2001, 52: 83-88.
- [3] Gao B, Meier PJ. Organic anion transport across the choroid plexus. *Microsc Res Tech* 2001, 52: 60-64.
- [4] Emerich DF, Vasconcellos AV, Elliott RB, Skinner SJ, Borlongan CV. The choroid plexus: function, pathology and therapeutic potential of its transplantation. *Expert Opin Biol Ther* 2004, 4: 1191-1201.
- [5] Emerich DF, Skinner SJ, Borlongan CV, Vasconcellos AV, Thanos CG. The choroid plexus in the rise, fall and repair of the brain. *Bioessays* 2005, 27: 262-274.
- [6] Colombo JA, Napp MI. Cerebrospinal fluid from L-dopa-treated Parkinson's disease patients is dystrophic for various neural cell types *ex vivo*: effects of astroglia. *Exp Neurol* 154, 1998: 452-463.
- [7] Hao R, Norgren RB, Lau YS, Pfeiffer RF. Cerebrospinal fluid of Parkinson's disease patients inhibits the growth and function of dopaminergic neurons in culture. *Neurology* 1995, 45: 138-142.
- [8] Alcazar A, Regidor I, Masjuan J, Salinas M, Alvarez-Cermeño JC. Induction of apoptosis by cerebrospinal fluid from patients with primary-progressive multiple sclerosis in cultured neurons. *Neurosci Lett* 1998, 255: 75-78.
- [9] Blevins JE, Stanley BG, Reidelberger RD. Brain regions where cholecystokinin suppresses feeding in rats. *Brain Res* 2000, 860: 1-10.
- [10] Männistö PT, Törnwall M, Tuomainen P, Borisenko SA, Tuominen RK. Effect of nitecapone and clorgyline, given intracerebro-ventricularly on L-dopa metabolism in the rat brain. *NeuroReport* 1992, 3: 641-644.
- [11] Araujo DM, Hilt DC. Glial cell line-derived neurotrophic factor attenuates the excitotoxin-induced behavioral and neurochemical deficits in a rodent model of Huntington's disease. *Neuroscience* 1997, 81: 1099-1110.
- [12] Lazorthes Y, Sagen J, Sallerin B, Tkaczuk J, Duplan H, Sol JC, *et al.* Human chromaffin cell graft into the CSF for cancer pain management: a prospective phase II clinical study. *Pain* 2000, 87: 19-32.
- [13] Tze WJ, Tai J. Intracerebral allotransplantation of purified pancreatic endocrine cells and pancreatic islets in diabetic rats. *Transplantation* 1984, 38: 107-111.
- [14] Tze WJ, Tai J. Intrathecal transplantation of single pancreatic endocrine cells. *Transplant Proc* 1987, 19 (1 Pt 2): 928-930.
- [15] Tze WJ, Tai J. Allotransplantation of dispersed single pancreatic endocrine cells in diabetic rats. *Diabetes* 1988, 37: 383-392.
- [16] Lee HC, Ahn KJ, Lim SK, Kim KR, Ahn YS, Lee KE, *et al.* Allotransplantation of rat islets into the cisterna magna of streptozotocin-induced diabetic rats. *Transplantation* 1992, 53: 513-516.
- [17] Carrithers MD, Visintin I, Viret C, Janeway CS Jr. Role of genetic background in P selectin-dependent immune surveillance of the central nervous system. *J Neuroimmunol* 2002, 129: 51-57.
- [18] Merskey H, Bogduk N (eds). *Classification of Chronic Pain*. Seattle: IASP press, 1994.
- [19] Bonica JJ. *Advances in Pain Research and Therapy*. New York: Raven Press, 1970, 141-166.

- [20] de Novellis V, Siniscalco D, Galderisi U, Fuccio C, Nolano M, Santoro L, *et al.* Neuropharmacology 2004, 46 : 468-479.
- [21] Décoster I, Buchser E, Gilliard N, Saydoff J, Zurn AD, Aebischer P. Intrathecal implants of bovine chromaffin cells alleviate mechanical allodynia in a rat model of neuropathic pain. Pain 1998, 76: 159-166.
- [22] Lu Y, Jing R, Yeomans DC, Pappas GD. Porcine chromaffin cells, culture, and transplant for antinociceptive effects in rodents and primates. Neurol Res 2004, 26: 707-712.
- [23] Eser Elçin A, Elçin YM, Pappas GD. Neural tissue engineering: adrenal chromaffin cell attachment and viability on chitosan scaffolds. Neurol Res 1998, 20: 648-654.
- [24] Kim YM, Jeon YH, Jin GC, Lim JO, Baek WY. Immunoisolated chromaffin cells implanted into the subarachnoid space of rats reduce cold allodynia in a model of neuropathic pain: a novel application of microencapsulation technology. Artif Organs 2004, 28: 1059-1066.
- [25] Nasiri Nezhad F, Sagen J. NMDA antagonist peptide supplementation enhances pain alleviation by adrenal medullary transplants. Cell Transplant 2005, 14: 203-211.
- [26] Joseph JM, Goddard MB, Mills J, Padrun V, Zurn A, Zielinski B, *et al.* Transplantation of encapsulated bovine chromaffin cells in the sheep subarachnoid space: a preclinical study for the treatment of cancer pain. Cell Transplant 1994, 3: 355-364.
- [27] Kaplan FA, Krueger PM, Harvey J, Goddard MB. Peripheral xenogeneic immunological response to encapsulated bovine adrenal chromaffin cells implanted within the sheep lumbar intrathecal space. Transplantation 1996, 61: 1215-1221.
- [28] Wu HH, Wilcox GL, McLoon SC. Implantation of AtT-20 or genetically modified AtT-20/hENK cells in mouse spinal cord induced antinociception and opioid tolerance. J Neurosci 1994, 14: 4806-4814.
- [29] Wu HH, Lester BR, Sun Z, Wilcox GL. Antinociception following implantation of mouse B16 melanoma cells in mouse and rat spinal cord. Pain 1994, 56: 203-210.
- [30] Wu HH, McLoon SC, Wilcox GL. Antinociception following implantation of AtT-20 and genetically modified AtT-20/hENK cells in rat spinal cord. J Neural Transplant Plast 1993, 4: 15-26.
- [31] Eaton MJ, Karmally S, Martinez MA, Plunkett JA, Lopez T, Cejas PJ. Lumbar transplant of neurons genetically modified to secrete galanin reverse pain-like behaviors after partial sciatic nerve injury. J Peripher Nerv Syst 1999, 4: 245-257.
- [32] Cejas PJ, Martinez M, Karmally S, McKillop M, McKillop J, Plunkett JA, *et al.* Lumbar transplant of neurons genetically modified to secrete brain-derived neurotrophic factor attenuates allodynia and hyperalgesia after sciatic nerve constriction. Pain 2000, 86: 195-210.
- [33] Eaton MJ, Plunkett JA, Karmally S, Martinez MA, Montanez K. Changes in GAD- and GABA- immunoreactivity in the spinal dorsal horn after peripheral nerve injury and promotion of recovery by lumbar transplant of immortalized serotonergic precursors. J Chem Neuroanat 1998, 16: 57-72.
- [34] Stubbley LA, Martinez MA, Karmally S, Lopez T, Cejas P, Eaton MJ. Only early intervention with gamma-aminobutyric acid cell therapy is able to reverse neuropathic pain after partial nerve injury. J Neurotrauma 2001, 18: 471-477.
- [35] Winn SR, Emerich DF. Managing chronic pain with encapsulated cell implants releasing catecholamines and endogenous opioids. Front Biosci 2005, 10: 367-378.
- [36] Eaton MJ, Wolfe SQ, Martinez M, Hernandez M, Furst C, Huang J, *et al.* Subarachnoid transplant of a human neuronal cell line attenuates chronic allodynia and hyperalgesia after excitotoxic spinal cord injury in the rat. J Pain 2007, 8: 33-50.
- [37] Xu Y, Tian XB, An K, Yang H, Tian YK. Lumbar transplantation of immortalized enkephalin-expressing astrocytes attenuates chronic neuropathic pain. Eur J Pain 2008, 12: 525-533.
- [38] Eaton M. Cell therapy for neuropathic pain in spinal cord injuries. Exp Opin Biol Ther 2004, 4: 1861-1869.
- [39] Ohta M, Suzuki Y, Noda T, Ejiri Y, Dezawa M, Kataoka K, *et al.* Bone marrow stromal cells infused into the cerebrospinal fluid promote functional recovery of the injured rat spinal cord with reduced cavity formation. Exp Neurol 2004, 187: 266-278.
- [40] Fuchs E, Segre JA. Stem cells: a new lease on life. Cell 2000, 100: 143-155.
- [41] Horner PJ, Gage FH. Regenerating the damaged central nervous system. Nature 2000, 407: 963-970.
- [42] Van-der-Kooy D, Weiss S. Why stem cells? Science 2000, 287: 1439-1441.
- [43] Andrews EM, Tsai SY, Johnson SC, Farrer JR, Wagner JP, Kopen GC, *et al.* Human adult bone marrow-derived somatic cell therapy results in functional recovery and axonal plasticity following stroke in the rat. Exp Neurol 2008, 211: 588-592.
- [44] Wu J, Sun Z, Sun HS, Wu J, Weisel RD, Keating A, *et al.* Intravenously administered bone marrow cells migrate to damaged brain tissue and improve neural function in ischemic rats. Cell Transplant 2008, 16: 993-1005.
- [45] Pearse DD, Sanchez AR, Pereira FC, Andrade CM, Puzis R, Pressman Y, *et al.* Transplantation of Schwann cells and/or olfactory ensheathing glia into the contused spinal cord: Survival, migration, axon association, and functional recovery. Glia 2007, 55: 976-1000.
- [46] Cui L, Jiang J, Wei L, Zhou X, Fraser JL, Snider BJ, *et al.* Transplantation of embryonic stem cells improves nerve repair and functional recovery after severe sciatic nerve axotomy in rats. Stem Cells 2008, 26: 1356-1365.
- [47] Brustle O, Choudhary K, Karra K, Hittner A, Murray K, Dubois-Dalcq M, *et al.* Chimeric brains generated by intraventricular transplantation of fetal human brain cells into embryonic rats. Nat Biotechnol 1998, 16: 1040-1044.
- [48] Ourednik V, Ourednik J, Flax JD, Zawada WM, Hutt C, Yang C, *et al.* Segregation of human neural stem cells in the developing primate forebrain. Science 2001, 293: 1820-1824.

- [49] Gao YM, Sun JH, Yang L. Survival and differentiation of embryonic neuroepithelial cells following transplantation into the lateral ventricle of rats. *Acta Anatomi Sin* 2002, 33: 475-478. (Chinese, English abstract)
- [50] Wu S, Suzuki Y, Kitada M, Kataoka K, Kitaura M, Chou H, *et al.* New method for transplantation of neurosphere cells into injured spinal cord through cerebrospinal fluid in rat. *Neurosci Lett* 2002, 318: 81-84.
- [51] Wu S, Suzuki Y, Kitada M, Kitaura M, Kataoka K, Takahashi J, *et al.* Migration, integration, and differentiation of hippocampus-derived neurosphere cells after transplantation into injured rat spinal cord. *Neurosci Lett* 2001, 312: 173-176.
- [52] Wu S, Suzuki Y, Noda T, Bai H, Kitada M, Kataoka K, *et al.* Immunohistochemical and electron microscopic study of invasion and differentiation in spinal cord lesion of neural stem cells grafted through cerebrospinal fluid in rat. *J Neurosci Res* 2002, 69: 940-945.
- [53] Ben-Hur T, Einstein O, Mizrahi-Kol R, Ben-Menachem O, Reinhartz E, Karussis D, *et al.* Transplanted multipotential neural precursor cells migrate into the inflamed white matter in response to experimental autoimmune encephalomyelitis. *Glia* 2003, 41: 73-80.
- [54] Bai HL, Wu SF, Suzuki Y. Early and dynamic distribution of the stem cells on the injured spinal cord following transplantation through the fourth ventricle. *J Xi'an Jiaotong Univ Med Sci* 2005, 26: 424-427. (Chinese, English abstract)
- [55] Firouzi M, Moshayedi P, Saberi H, Mobasheri H, Abolhassani F, Jahanzad I, *et al.* Transplantation of Schwann cells to subarachnoid space induces repair in contused rat spinal cord. *Neurosci Lett* 2006, 402: 66-70.
- [56] Bernstein JJ, Karp SM, Goldberg WJ, DeGiorgio LA, Blass JP. Human leptomeningeal-derived cells express GFAP and HLADR when grafted into rat spinal cord. *Int J Dev Neurosci* 1996, 14: 681-687.
- [57] Satake K, Lou J, Lenke LG. Migration of mesenchymal stem cells through cerebrospinal fluid into injured spinal cord tissue. *Spine* 2004, 29: 1971-1979.
- [58] Wu S, Suzuki Y, Ejiri Y, Noda T, Bai H, Kitada M, *et al.* Bone marrow stromal cells enhance differentiation of cocultured neurosphere cells and promote regeneration of injured spinal cord. *J Neurosci Res* 2003, 72: 343-351.
- [59] Seledtsov VI, Rabinovich SS, Parlyuk OV, Poveshchenko OV, Astrakov SV, Samarin DM, *et al.* Cell therapy of comatose states. *Bull Exp Biol Med* 2006, 142: 129-132.
- [60] Xie ZW, Cui GX, Li YZ, Li BW, Zhu SW, Song CZ, *et al.* Curative effect of autologous mesenchymal stem cell transplantation on spinal cord injury. *J Clin Rehabil Tissue Eng Res* 2007, 11: 1277-1279. (Chinese, English Abstract)
- [61] Saito F, Nakatani T, Iwase M, Maeda Y, Hirakawa A, Murao Y, *et al.* Spinal cord injury treatment with intrathecal autologous bone marrow stromal cell transplantation: the first clinical trial case report. *J Trauma* 2008, 64: 53-59.
- [62] Bai H, Suzuki Y, Noda T, Wu S, Kataoka K, Kitada M, *et al.* Dissemination and proliferation of neural stem cells on the spinal cord by injection into the rat: a method for cell transplantation. *J Neurosci Methods* 2003, 124: 181-187.

脑脊液内细胞移植治疗脊髓损伤

刘彦¹, 黄红云^{1,2,3}

¹北京市虹天济神经科学研究院脊髓损伤研究组, 北京 100144

²北京康复中心神经外科, 北京 100144

³泰山医学院神经科学研究所, 北京 100144

摘要: 经脑脊液进行细胞移植治疗脊髓损伤具有较大的临床应用前景。有关研究显示, 经脑脊液进行的细胞移植方法安全、方便, 对病人的损伤小, 适用于治疗中枢神经系统多发疾病。但是经脑脊液移植的细胞能否促进中枢神经系统轴突再生和脊髓神经功能修复仍存在争议, 其作用机制、移植时间以及移植细胞种类方面还需要进一步研究。本文对经脑脊液细胞移植方法用于治疗脊髓损伤进行综述, 探讨此方法对脊髓损伤后中枢神经系统内轴突再生及功能修复的促进作用。

关键词: 细胞移植; 脑脊液; 蛛网膜下腔