Review Article

Administration of Olfactory Ensheathing Cells to Relieve the Symptoms of Spinal Cord Injury

Da-Chuan Yeh[1#], Hui-Ping Lin[2#], Chih-Pin Chuu[2], Shinn-Zong Lin[3] and Tzu-Min Chan[4,5*]

[1]Department of Internal Medicine, China Medical University Beigan Hospital, Yunlin, Taiwan, ROC

[2]Institute of Cellular and System Medicine, National Health Research Institutes, Miaoli 35053, Taiwan, ROC

[3]Center for Neuropsychiatry, China Medical University Hospital, Taichung 40447, Taiwan, ROC

[4]Department of Medical Education and Research, China Medical University Beigan Hospital, Yunlin, Taiwan, ROC

[5]Department of Medical Education and Research, China Medical University An-Nan Hospital, Tainan, Taiwan, ROC

[#]The authors provided equal contributions

[*]Corresponding author: Tzu-Min Chan, Department of Medical Education and Research, China Medical University Beigang Hospital, 123 Shin Der Road, Beigang, Yun Lin 651, Taiwan, ROC, Tel: 886-5-7837901, Ext. 1213; Fax: 886-5-7836439; E-mail: ziv.j@yahoo.com.tw

Abstract

Spinal cord injury (SCI) is a challenging issue for scientists and clinicians. Thus far, no treatments capable of relieving symptoms associated with neuronal loss and functional defects have been developed. However, stem cell therapy has demonstrated considerable promise in overcoming neuronal cell death and glial scarring in the area of damage associated with SCI. A number of studies have demonstrated the therapeutic advantages and clinical applicability of olfactory ensheathing cells (OECs) in neurodegenerative disorders. This review focuses on the potential benefits of OECs in an SCI animal model and examines partial successes that have been achieved in human clinical trials. We also discuss methods that could further enhance the therapeutic efficacy of these efforts, such as modifying the extracellular matrix to ensure appropriate differentiation and prolong the survival of transplanted cells; and further in situ altering of the spinal cord niche to facilitate the completely therapy of OECs in SCI.

Keywords: Spinal cord injury; Olfactory ensheathing cell; Niche; Extracellular matrix

Introduction

Between 10,000 and 14,000 spinal cord injury (SCI) are reported every year in the United States [1], and medical treatments that deal with acute SCI and subsequent complications are extremely expensive. Following the occurrence of SCI, there is a therapeutic window in which the devastating outcomes of secondary injury can be improved [2]. Therapeutic schemes implemented in response to SCI can be divided into two categories: 1) prevention or amelioration of secondary injury and 2) regenerative intervention. At present, there are no therapeutic methods capable of promoting the complete recovery of neurological damage resulting from SCI. Nonetheless, several research teams have reported limited recoveries through the transplantation of pluripotent cells; therefore, stem cells are being widely studied to develop strategies for the regenerative treatment of SCI [3].

Neuronal cell death is the major pathogenetic mechanism of various neurological disorders, including SCI disorder; therefore, stem cell therapy is a promising strategy to replace injured cells through regeneration [4]. The effectiveness of transplanting embryonic stem cells in patients suffering from neurodegenerative disorders, such as Parkinson's [5], Huntington's [6], and SCI has been investigated [7]. However, logistical and ethical considerations have presented challenges to further therapeutic developments in this area, raising the clinical applicability of autologous stem cells [8]. Peripheral stem cells (PSCs) can be isolated from various tissues, such as bone marrow, adipose tissue, umbilical cord blood, muscles, corneal stroma, tooth buds, and nasal mucosa, thereby providing an alternative source for use in transplantation medicine [9,10]. The preparation of autologous stem cells may be an appropriate strategy for clinical applications, as there is no need for in vitro extension and because these cells can be cultured in serum free conditions [11].

Various strategies have been developed for the treatment of animals with SCI, such as adding growth factors [12], providing peripheral nerve or embryonic tissue [13], and transplanting Schwann cells [14]. Recent studies have shown that olfactory ensheathing cells (OECs) have therapeutic potential to enhance axonal restoration and repair in demyelinating-related disorders [15,16]. Previous researchers have further highlighted the therapeutic potential of OECs in neurodegenerative disorders including SCI; however, the mechanisms underlying neural regeneration have yet to be elucidated [16,17]. This review presents information currently available on SCI and OECs, summarizes the potential therapeutic effects of OECs in SCI animal models and human clinical trials, and discusses various potential molecular mechanisms.

OECs

OECs are found in the olfactory bulb and olfactory mucosa in the vicinity of the lamina propria. In animal neurodegenerative disorders, they are believed to induce neurotrophic effects similar to those of Schwann cells [18]. The olfactory mucosa are stimulated by a variety of external environmental variables. As a result, they are under perpetual

threat of damage and constantly being repaired. Nonetheless, the fact that the sense of smell is rarely lost throughout this process of injury and repair can be attributed to the constant regeneration of olfactory nerve cells [19]. More specifically, the olfactory mucosa is constantly renewed through OECs which are capable of supporting neurogenesis throughout life [20,21]. Nerve cells projected from the nasal mucosa are directed to olfactory nerves associated with the central nervous system [22].

As demonstrated in previous studies, the olfactory mucosa includes unmyelinated olfactory nerves with OECs and sheet-like processes of olfactory nerve fibroblasts [23,24]. The OECs enable the growth of axons from the neurons of the olfactory mucosa to reinnervate the olfactory bulb and in turn form synapses in the brain [17]. The neuroregenerative ability OECs through axonal outgrowth has shown promise in the treatment of SCI in relevant animal models [25]. Furthermore, a number of investigations have shown that OECs can play an important role in the recovery of bladder function and phrenic nerve activity following SCI [3]. This makes OECs a useful type of pluripotent cell for transplantation, capable of facilitating nerve regeneration in SCI patients.

SCI

The spinal cord contains neuronal cell bodies and serves as a conduit connecting motor and sensory information, which is necessary for neurotransmission between the brain and the body [26]. In component of spinal cord include neuron cells and the axon of long nerve fibers [27]. Axonal conduction follows either a downward or upward path, carrying signals to and from the brain [28]. Most axonal pathways are insulated by a white sheath called myelin, otherwise known as white matter. Neuronal trees have branches called dendrites, which receive signals from other nerve cells, constitute gray matter, located in the center of the spinal disc as a butterfly shaped region.

SCI refers to spinal cord damage and is more commonly caused by trauma than disease [29]. Traumatic injuries to the vertebrae often result from accidents, such as motor vehicle mishaps, falls, acts of violence, and recreational injuries. SCI may also be caused by infection or inflammation in the region of the spinal tissue, as well as polio, spina bifida, transverse myelitis, and multiple sclerosis [30]. If damage occurs longitudinally across the spinal tract, SCI can lead to the loss of nerve function [31]. Without effective treatment, the neurological deficits of SCI can have long-term effects for the patient, the family, and society as a whole [32].

OEC application in SCI treatment

The traditional view that the central nervous system injury due to poor intrinsic and extrinsic environmental regeneration inhibition, resulting in damage axons cannot regenerate [33]. Recent discoveries have moved the transplantation of OECs to the forefront of SCI treatments [34]. OCEs have attracted considerable attention because the unique nature of these cells can promote nerve regeneration and the recovery of nerve function in the spinal cord. Besides, transplantation of OECs into the injured spinal cord display an excellent regenerative effects mediated through reorganize the glial scar, remyelinate axons and stimulate blood vessel formation [35]. According to the results of behavioral examinations, OEC transplantation can provide considerable improvement in functional recovery following SCI (Table 1) [36-48]. Use of OECs transplantation obtained axonal regeneration, although it looks mildly progressive, might provide an adequate foundation for the functional benefits [38].

Diseases	Type	Model	Symptom improvement	Note
SCI relevant [36]	Primarily cultured rat OECs	T8 spinal cord crush injury	Significant improve BBB scores after OECs transplantation	Combined with chondroitinase ABC
			Reduced gross area of necrosis	
SCI relevant [37]	GDNF modified OECs	Thoracic spinal cord transection injury	Lots of confused and disorderly regenerated axons	Combined with axonal growth inhibiting protein antibody (IN-1)
			Restored motor activity	
			Improve survival and regeneration of the injured axons	
SCI relevant [38]	OECs were isolated from the olfactory bulbs of adult rats	Spinal cord transection at T9	Improved hindlimb locomotor function	Combined with neural stem cells
			New nerve fibers across the injured region	
SCI relevant [39]	Primarily cultured rat OECs	C4 hemisection in adult rats	Enhanced axonal growth nor prevented retrograde cell death	OECs were transplanted into the lateral funiculus at 1 mm rostral and caudal to the transection site
			Support neuronal survival and regeneration after spinal cord injury	
SCI relevant [40]	Human OECs	lateral T8 hemisection of the spinal cord	Motor functions steadily increased	involvement together with Schwann cells into remyelination of regenerating axons
SCI relevant [41]	Primarily cultured rat OECs	T4 spinal cord transection	Reduce duration of autonomic dysreflexia	

			Increased dendritic length of preganglionic neurons	
SCI relevant [42]	Primarily cultured rat OECs	A balloon-induced compressive lesion was used to produce SCI in rats	Improvement of hindlimb function	Co-transplantation of olfactory ensheathing glia and mesenchymal stromal cells
			Modest recovery in amplitude following transplantation	
SCI relevant [43]	Primarily cultured rat OECs	Rat SCI models were created with cushion forces	Behavioral evaluation showed an improvement	Co-transplantation of human bone marrow stromal cells
			Larger numbers and sizes of axon bundles	
SCI relevant [44]	embryonic, neonatal, and adult rats OECs	Toxin-induced model of spinal cord demyelination	Remyelinate is most efficiently achieved by embryonic-derived OECs	To search the optimal donor age for OEC associated remyelination
Human SCI [45]	Autologous human OECs	chronic thoracic paraplegia	Improvement in spinal cord transmission and activity of lower extremity muscles	
Human SCI [46]	Autologous human OECs	Patients with cervical SCI of >6 months' duration	Improved substantial sensation and motor activity	No serious complications postoperatively or during the follow-up period
			Bladder function was restored in two patients	
Human SCI [47]	Autologous human OECs	lesions ranging from 1 to 6 cm that were present at C4–T6 neurological levels	Improved in their ASIA sensory neurological scores	
Abbreviation: BBB (Basso, Beattie, and Bresnahan), T8 (Thoracic 8), C4 (Cervical 4), ASIA (American Spinal Injury Association)				

Table 1: OECs applications upon SCI in the past few years.

Previous results from clinical trials have also confirmed that OECs can be helpful in neurological recovery and relieving the symptoms of SCI [46]. When OECs are transplanted into the demyelinated spinal cord, these cells help to repair defective myelin and improve the conductance of the remyelinated axons. Other researchers have demonstrated the ability of OECs to promote the regeneration of axons in the vicinity of spinal cord lesions. Additionally, the safety and feasibility of autologous mucosal OECs transplantation have been widely addressed in SCI patients (Table 1). No adverse effects related to the transplantation of OECs have been observed, and no indication of neurological exacerbation, neuropathic pain, neuroinfection or tumorigenesis has been reported [45].

Molecular Signalling

The molecular mechanisms involved in the treatment of OECs have been investigated with regard to neurotrophins, extracellular matrices, ligands, transcriptional coactivators, and other factors [18]. Neurotrophins have demonstrated benefits in prolonging the survival of neurons and axonal expansion. Many neurotrophins secreted from hOECs/ONFs, such as BDNF [47], VEGF [49] and GDNF [50], have been studied extensively to determine whether they play a role in facilitating cerebral plasticity and improving functional rehabilitation in SCI animal models. In recent reports, stromal cells have been used to derive factor-1. Its receptor, CXCR4 (SDF-1/CXCR4), has been shown to provide generalized trophic support to neuronal cells and assist in the repair of the spinal cord [17]. SDF-1 is a CXC chemokine generated by mesenchymal stem cells. This chemokine is a potent chemo-attractant for hematopoietic stem cells that are constitutively expressed by peripheral tissue [17].

Future Expectations

For more effective therapeutic potentials of the extracellular matrix (ECM) approach has been deemed a suitable method to control the fate of stem cells, prolong cell survival, and promote differentiation into neuronal precursors [51,52]. Research has indicated that ECM, such as functional three-dimensional scaffolds and microenvironment factors assembled into a matrix, are correlated with neuron-like cells differentiation [53]. In addition, cells cultured in vitro in ECM have demonstrated the ability to perform the standard functions of neuron cells and also have therapeutic potential in relevant animal models. These findings support the applicability of the ECM cultured cells in the treatment of SCI.

The ECM can be remodeled to create a niche that controls the differentiation outcomes and inhibits undifferentiated transplanted cells. Thus, directly programming endogenous stem cells into tissue-specific lineages may be an achievable goal [54]. The alteration of ECM in situ has demonstrated considerable potential to increase the survival and differentiation rate of transplanted cells, thereby enhancing the effectiveness of cell-based therapies [55,56]. A finely defined microenvironment is likely able to provide endogenous undifferentiated stem cells (including transplanted undifferentiated stem cells) with a suitable niche for differentiation [57]. Autologous hematopoietic stem cells (HSCs) are known to exist in bone marrow and have the capacity to differentiate into most cell lines. However, they rarely end up in peripheral tissue, where endogenous PSCs are already scarce [58]. Additionally, granulocyte colony-stimulating factors (GCSFs) are widely applied to mobilize HSCs in many types of treatments. Thus, therapies combining the use of GCSFs could be adopted to transport HSCs to tissues requiring treatment [59,60]. Other studies have demonstrated that the combination of defined

transcription factors has the ability to convert somatic cells directly into functional nerve cells and does not require iPS cells fate, to reduce tumorigenic potential [61]. In summary, in situ alteration of the extracellular matrix to direct the programming/reprogramming of endogenous cells is a promising method for the treatment of SCI.

References

1. Bartolomei JC, Greer CA (2000) Olfactory ensheathing cells: bridging the gap in spinal cord injury. Neurosurgery 47: 1057-1069.

2. Piltti KM, Salazar DL, Uchida N, Cummings BJ, Anderson AJ (2013) Safety of human neural stem cell transplantation in chronic spinal cord injury. Stem Cells Transl Med 2: 961-974.

3. Féron F, Perry C, Cochrane J, Licina P, Nowitzke A, et al. (2005) Autologous olfactory ensheathing cell transplantation in human spinal cord injury. Brain 128: 2951-2960.

4. Ronaghi M, Erceg S, Moreno-Manzano V, Stojkovic M (2010) Challenges of stem cell therapy for spinal cord injury: human embryonic stem cells, endogenous neural stem cells, or induced pluripotent stem cells? Stem Cells 28: 93-99.

5. Daadi MM, Grueter BA, Malenka RC, Redmond DE Jr, Steinberg GK (2012) Dopaminergic neurons from midbrain-specified human embryonic stem cell-derived neural stem cells engrafted in a monkey model of Parkinson's disease. PLoS One 7: e41120.

6. Bradley CK, Scott HA, Chami O, Peura TT, Dumevska B, et al. (2011) Derivation of Huntington's disease-affected human embryonic stem cell lines. Stem Cells Dev 20: 495-502.

7. Bretzner F, Gilbert F, Baylis F, Brownstone RM (2011) Target populations for first-in-human embryonic stem cell research in spinal cord injury. Cell Stem Cell 8: 468-475.

8. Taylor CJ, Bolton EM, Bradley JA (2011) Immunological considerations for embryonic and induced pluripotent stem cell banking. Philos Trans R Soc Lond B Biol Sci 366: 2312-2322.

9. Mani SA, Guo W, Liao MJ, Eaton EN, Ayyanan A, et al. (2008) The epithelial-mesenchymal transition generates cells with properties of stem cells. Cell 133: 704-715.

10. Méndez-Ferrer S, Michurina TV, Ferraro F, Mazloom AR, Macarthur BD, et al. (2010) Mesenchymal and haematopoietic stem cells form a unique bone marrow niche. Nature 466: 829-834.

11. Dolgin E (2011) Stem cells: Transplants on trial. Nature 480: S46-47.

12. Awad BI, Carmody MA, Steinmetz MP3 (2013) Potential Role of Growth Factors in the Management of Spinal Cord Injury. World Neurosurg 9: 1520-1524.

13. Myckatyn TM, Mackinnon SE, McDonald JW (2004) Stem cell transplantation and other novel techniques for promoting recovery from spinal cord injury. Transpl Immunol 12: 343-358.

14. Guest J, Santamaria AJ, Benavides FD (2013) Clinical translation of autologous Schwann cell transplantation for the treatment of spinal cord injury. Curr Opin Organ Transplant 18: 682-689.

15. Kocsis JD, Akiyama Y, Radtke C (2004) Neural precursors as a cell source to repair the demyelinated spinal cord. J Neurotrauma 21: 441-449.

16. Li L, Adnan H, Xu B, Wang J, Wang C, et al. (2014) Effects of transplantation of olfactory ensheathing cells in chronic spinal cord injury: a systematic review and meta-analysis. Eur Spine J

17. Shyu WC, Liu DD, Lin SZ, Li WW, Su CY, et al. (2008) Implantation of olfactory ensheathing cells promotes neuroplasticity in murine models of stroke. J Clin Invest 118: 2482-2495.

18. Chiu SC, Hung HS, Lin SZ, Chiang E, Liu DD (2009) Therapeutic potential of olfactory ensheathing cells in neurodegenerative diseases. J Mol Med (Berl) 87: 1179-1189.

19. Yui S, Ito D, Fujita N, Nishimura R (2011) Effects of fibroblasts derived from the olfactory bulb and nasal olfactory mucosa on proliferation of olfactory ensheathing cells harvested from the olfactory bulb. J Vet Med Sci 73: 133-137.

20. Barnett SC, Roskams AJ (2008) Olfactory ensheathing cells: isolation and culture from the neonatal olfactory bulb. Methods Mol Biol 438: 85-94.

21. Wang L, Yang P, Liang X, Ma L, Wei J (2014) [Comparison of therapeutic effects of olfactory ensheathing cells derived from olfactory mucosa or olfactory bulb on spinal cord injury mouse models]. Xi Bao Yu Fen Zi Mian Yi Xue Za Zhi 30: 379-383.

22. Choi D, Li D, Law S, Powell M, Raisman G (2008) A prospective observational study of the yield of olfactory ensheathing cells cultured from biopsies of septal nasal mucosa. Neurosurgery 62: 1140-1144.

23. Lindvall O, Kokaia Z, Martinez-Serrano A (2004) Stem cell therapy for human neurodegenerative disorders-how to make it work. Nat Med 10 Suppl: S42-50.

24. Taguchi A, Soma T, Tanaka H, Kanda T, Nishimura H, et al. (2004) Administration of CD34+ cells after stroke enhances neurogenesis via angiogenesis in a mouse model. J Clin Invest 114: 330-338.

25. Barinaga M (2000) Fetal neuron grafts pave the way for stem cell therapies. Science 287: 1421-1422.

26. Rabchevsky AG, Patel SP, Duale H, Lyttle TS, O'Dell CR, et al. (2011) Gabapentin for spasticity and autonomic dysreflexia after severe spinal cord injury. Spinal Cord 49: 99-105.

27. Tysseling VM, Sahni V, Pashuck ET, Birch D, Hebert A, et al. (2010) Self-assembling peptide amphiphile promotes plasticity of serotonergic fibers following spinal cord injury. J Neurosci Res 88: 3161-3170.

28. Côté MP, Hanna A, Lemay MA, Ollivier-Lanvin K, Santi L, et al. (2010) Peripheral nerve grafts after cervical spinal cord injury in adult cats. Exp Neurol 225: 173-182.

29. Kakinohana M, Kida K, Minamishima S, Atochin DN, Huang PL, et al. (2011) Delayed paraplegia after spinal cord ischemic injury requires caspase-3 activation in mice. Stroke 42: 2302-2307.

30. Trebst C, Raab P, Voss EV, Rommer P, Abu-Mugheisib M, et al. (2011) Longitudinal extensive transverse myelitis--it's not all neuromyelitis optica. Nat Rev Neurol 7: 688-698.

31. Lin CS, Macefield VG, Elam M, Wallin BG, Engel S, et al. (2007) Axonal changes in spinal cord injured patients distal to the site of injury. Brain 130: 985-994.

32. Coleman JA, Harper LA, Perrin PB, Olivera SL, Perdomo JL, et al. (2013) Examining the relationship between health-related quality of life in individuals with spinal cord injury and the mental health of their caregivers in Colombia, South America. Int J Rehabil Res 36: 308-314.

33. Blizzard CA, King AE, Haas MA, O'Toole DA, Vickers JC, et al. (2009) Axonal shearing in mature cortical neurons induces attempted regeneration and the reestablishment of neurite polarity. Brain Res 1300: 24-36.

34. Ibarra A, Martiñón S (2009) Pharmacological approaches to induce neuroregeneration in spinal cord injury: an overview. Curr Drug Discov Technol 6: 82-90.

35. Roet KC, Verhaagen J2 (2014) Understanding the neural repair-promoting properties of olfactory ensheathing cells. Exp Neurol 261: 594-609.

36. Zhang C, He X, Lan B, Li H (2009) [Study on repair of subacute spinal cord injury by transplantation of olfactory ensheathing cells combined with chondroitinase ABC in adult rats]. Zhongguo Xiu Fu Chong Jian Wai Ke Za Zhi 23: 8-13.

37. Yan HB, Zhang ZM, Jin DD, Wang XJ, Lu KW (2009) [The repair of acute spinal cord injury in rats by olfactory ensheathing cells graft modified by glia cell line-derived neurotrophic factor gene in combination with the injection of monoclonal antibody IN-1]. Zhonghua Wai Ke Za Zhi 47: 1817-1820.

38. Wang G, Ao Q, Gong K, Zuo H, Gong Y, et al. (2010) Synergistic effect of neural stem cells and olfactory ensheathing cells on repair of adult rat spinal cord injury. Cell Transplant 19: 1325-1337.

39. Novikova LN, Lobov S, Wiberg M, Novikov LN (2011) Efficacy of olfactory ensheathing cells to support regeneration after spinal cord injury is influenced by method of culture preparation. Exp Neurol 229: 132-142.

40. Masgutova GA, Savchenko EA, Viktorov IV, Masgutov RF, Chelyshev YA (2010) Reaction of oligoglia to spinal cord injury in rats and transplantation of human olfactory ensheathing cells. Bull Exp Biol Med 149: 135-139.

41. Kalincík T, Choi EA, Féron F, Bianco J, Sutharsan R, et al. (2010) Olfactory ensheathing cells reduce duration of autonomic dysreflexia in rats with high spinal cord injury. Auton Neurosci 154: 20-29.

42. Amemori T, Jendelová P, Růzicková K, Arboleda D, Syková E (2010) Co-transplantation of olfactory ensheathing glia and mesenchymal stromal cells does not have synergistic effects after spinal cord injury in the rat. Cytotherapy 12: 212-225.

43. Deng YB, Liu Y, Zhu WB, Bi XB, Wang YZ, et al. (2008) The co-transplantation of human bone marrow stromal cells and embryo olfactory ensheathing cells as a new approach to treat spinal cord injury in a rat model. Cytotherapy 10: 551-564.

44. Coutts DJ, Humphries CE, Zhao C, Plant GW, Franklin RJ (2013) Embryonic-derived olfactory ensheathing cells remyelinate focal areas of spinal cord demyelination more efficiently than neonatal or adult-derived cells. Cell Transplant 22:1249-1261.

45. Tabakow P, Jarmundowicz W, Czapiga B, Fortuna W, Miedzybrodzki R, et al. (2013) Transplantation of autologous olfactory ensheathing cells in complete human spinal cord injury. Cell Transplant 22: 1591-1612.

46. Rao Y, Zhu W, Liu H, Jia C, Zhao Q, et al. (2013) Clinical application of olfactory ensheathing cells in the treatment of spinal cord injury. J Int Med Res 41: 473-481.

47. Lima C, Pratas-Vital J, Escada P, Hasse-Ferreira A, Capucho C, et al. (2006) Olfactory mucosa autografts in human spinal cord injury: a pilot clinical study. J Spinal Cord Med 29: 191-203.

48. Lang BC, Zhang Z, Lv LY, Liu J, Wang TY, et al. (2013) OECs transplantation results in neuropathic pain associated with BDNF regulating ERK activity in rats following cord hemisection. BMC Neurosci 14: 80.

49. Lopez-Vales R, Garcia-Alias G, Fores J, Navarro X, Verdu E (2004) Increased expression of cyclo-oxygenase 2 and vascular endothelial growth factor in lesioned spinal cord by transplanted olfactory ensheathing cells. J Neurotrauma 21:1031-1043.

50. Wang B, Han J, Gao Y, Xiao Z, Chen B, et al. (2007) The differentiation of rat adipose-derived stem cells into OEC-like cells on collagen scaffolds by co-culturing with OECs. Neurosci Lett 421: 191-196.

51. Browne S, Fontana G, Rodriguez BJ, Pandit A (2012) A protective extracellular matrix-based gene delivery reservoir fabricated by electrostatic charge manipulation. Mol Pharm 9: 3099-3106.

52. Raghavan S, Gilmont RR, Bitar KN (2013) Neuroglial differentiation of adult enteric neuronal progenitor cells as a function of extracellular matrix composition. Biomaterials 34: 6649-6658.

53. Chen EY, Wang YC, Mintz A, Richards A, Chen CS, et al. (2012) Activated charcoal composite biomaterial promotes human embryonic stem cell differentiation toward neuronal lineage. J Biomed Mater Res A 100: 2006-2017.

54. Malinowski M, Pietraszek K, Perreau C, Boguslawski M, Decot V, et al. (2012) Effect of lumican on the migration of human mesenchymal stem cells and endothelial progenitor cells: involvement of matrix metalloproteinase-14. PLoS One 7: e50709.

55. Kisseleva T, Brenner DA (2012) The phenotypic fate and functional role for bone marrow-derived stem cells in liver fibrosis. J Hepatol 56: 965-972.

56. Zurita M, Otero L, Aguayo C, Bonilla C, Ferreira E, et al. (2010) Cell therapy for spinal cord repair: optimization of biologic scaffolds for survival and neural differentiation of human bone marrow stromal cells. Cytotherapy 12: 522-537.

57. Ang XM, Lee MH, Blocki A, Chen C, Ong LL, et al. (2014) Macromolecular crowding amplifies adipogenesis of human bone marrow-derived mesenchymal stem cells by enhancing the pro-adipogenic microenvironment. Tissue Eng Part A 20: 966-981.

58. Fathke C, Wilson L, Hutter J, Kapoor V, Smith A, et al. (2004) Contribution of bone marrow-derived cells to skin: collagen deposition and wound repair. Stem Cells 22: 812-822.

59. Papayannopoulou T1 (2004) Current mechanistic scenarios in hematopoietic stem/progenitor cell mobilization. Blood 103: 1580-1585.

60. Shyu WC, Lin SZ, Yang HI, Tzeng YS, Pang CY, et al. (2004) Functional recovery of stroke rats induced by granulocyte colony-stimulating factor-stimulated stem cells. Circulation 110: 1847-1854.

61. Han DW, Tapia N, Hermann A, Hemmer K, Höing S, et al. (2012) Direct reprogramming of fibroblasts into neural stem cells by defined factors. Cell Stem Cell 10: 465-472.