World Journal of Stem Cells

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.4252/wjsc.v7.i1.186

World J Stem Cells 2015 January 26; 7(1): 186-194
ISSN 1948-0210 (online)
© 2015 Baishideng Publishing Group Inc. All rights reserved.

MINIREVIEWS

Stem cells for spine surgery

Joshua Schroeder, Janina Kueper, Kaplan Leon, Meir Liebergall

Joshua Schroeder, Kaplan Leon, Meir Liebergall, Department of Orthopedic Surgery, Spine Surgery, Hadassah Medical Center, Kiryat Hadassah, Jerusalem 91120, Israel
Janina Kueper, Department of Orthopedic Surgery, Spine and Scoliosis Service, Hospital for Special Surgery, Weill Cornell Medical College, New York, NY 10021, United States
Author contributions: All authors contributed to this paper.
Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/
Correspondence to: Joshua Schroeder, MD, Department of Orthopedic Surgery, Spine Surgery, Hadassah Medical Center, Kiryat Hadassah, POB 12000, Jerusalem 91120, Israel. schroeder.josh@gmail.com
Telephone: +972-50-4048134
Fax: +1212-606-1746
Received: July 28, 2014
Peer-review started: July 30, 2014
First decision: September 4, 2014
Revised: October 8, 2014
Accepted: October 28, 2014
Article in press: December 16, 2014
Published online: January 26, 2015

Abstract

In the past few years, stem cells have become the focus of research by regenerative medicine professionals and tissue engineers. Embryonic stem cells, although capable of differentiating into cell lineages of all three germ layers, are limited in their utilization due to ethical issues. In contrast, the autologous harvest and subsequent transplantation of adult stem cells from bone marrow, adipose tissue or blood have been experimentally utilized in the treatment of a wide variety of diseases ranging from myocardial infarction to Alzheimer's disease. The physiologic consequences of stem cell transplantation and its impact on functional recovery have been studied in countless animal models and select clinical trials. Unfortunately, the bench to bedside translation of this research has been slow. Nonetheless, stem cell therapy has received the attention of spinal surgeons due to its potential benefits in the treatment of neural damage, muscle trauma, disk degeneration and its potential contribution to bone fusion.

Key words: Stem cell; Spine surgery; Spinal cord injury; Peripheral nerve damage; Intervertebral disk regeneration; Fusion; Skeletal muscle regeneration

© The Author(s) 2015. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Stem cells have become an increasingly feasible option for the future treatment of spinal disorders. Recent scientific advances have allowed researchers and spinal surgeons alike to investigate the potential of stem cells in the regeneration of degenerated disks, healing spinal cord injury and helping bone growth in spinal fusion.

Schroeder J, Kueper J, Leon K, Liebergall M. Stem cells for spine surgery. *World J Stem Cells* 2015; 7(1): 186-194 Available from: URL: http://www.wjgnet.com/1948-0210/full/v7/i1/186.htm DOI: http://dx.doi.org/10.4252/wjsc.v7.i1.186

INTRODUCTION

In recent years, stem cells have become a focus of regenerative medicine. Adult stem cells, harvested directly from bone marrow, adipose tissue or blood have the ability to undergo mitosis as well as multipotent differentiation into a variety of cell lineages. The goal of stem cell therapy is to replace or replenish diseased tissue through the localized differentiation of transplanted stem cells into cells which advance the healing process or directly restore the tissue physically. Despite the years of research elucidating the physiology and the processes of stem cell differentiation, both the survival as well as the physical

and biochemical control over the stem cells when implanted into a body remains a challenge. Advances in material sciences have aided tremendously in providing a three-dimensional environment for the cells within a scaffold which allows for both the local retention of cells where they are intended to operate and simultaneously allowing the diffusion of nutrients to enable cell survival. Advances in genetic engineering on the other hand have allowed the modification of stem cells to induce the expression of selective growth factors to further aid in tissue reconstruction. Several challenges in spine surgery have been addressed by experimental ventures into stem cell therapy. Degenerative spinal disorders such as Degenerative Disk Disease have been sought to be addressed through the biological reconstruction of the disk by a variety of stem cells and growth factors, thereby potentially circumventing the need for surgery. The potentially devastating consequences of Spinal Cord Injury have been moderated through the implantation of stem cells to aid in the recovery of nerve cells. Spine surgery itself has been the focus of tissue engineers primarily to achieve bony fusion in the spinal fusion of vertebrae to attain stability. The iatrogenic injury of peripheral nerves and skeletal muscle surrounding the spine, which inevitably occurs during spine surgery whilst access to the spine is being prepared, although not as dramatic in its effect on the disability of the patient in the long-term has been addressed by many scientists. Overall, stem cell therapy, despite being in the experimental phase in most sub-disciplines, promises exciting opportunities to improve spine care and decrease the morbidity due to spine surgery in the future.

APPLICATION OF STEM CELLS IN SPINE SURGERY

Spine fusion

Spine fusion is performed to address the pain, deformity or neurologic deficit caused by degenerative conditions, spinal tumor, vertebral fractures and spinal deformities such as scoliosis and kyphosis amongst other indications. The bony fusion between two or more vertebrae eliminates the pain caused by aberrant motion of the vertebrae through immobilization. Lumbar fusion has been reported to have increased at a rate of 220% from 1990, more than the increases for knee and hip arthroplasty combined[1]. Ambulatory lumbar spine surgery has been demonstrated to increase at a larger rate relative to inpatient surgery[2]. Cervical and thoracolumbar fusions have also reportedly increased at a rate of 89% and 31%, respectively, mirroring the rapid increase in the utilization of the procedure[3]. The introduction of new surgical technology has not proven to reduce reoperation rates[4]. The vital elements in bony fusion are an adequate quantity of bone-forming cells (osteogenesis), an appropriate microenvironment directing bone synthesis through a variety of growth factors (osteoinduction), and a scaffold or cage in which the growth of bone is well positioned (osteoconduction). Despite the recent advances in cage design and bone fusion extender materials, pseudoarthrosis remains a pressing issue occurring in 13%-41.4% of patients[5-8]. Risk factors for pseudoarthrosis have been reported to be older age, thoracolumbar kyphosis, smoking, diabetes mellitus, metabolic bone disease and female gender[6,8-11]. As patients more than 60 years old represent the demographic with the largest increase in the rate of fusion surgery, the medical community has begun investigating alternatives to support the process of bone growth and fusion, for example with the implantation of stem cells[1]. The gold standard for creating a bony fusion is the use of autograft bone from the iliac crest; however, this has been associated with increased morbidity. Allograft or synthetic bone graft extenders carry the osteoconductive, and to a different extent, the osteoinductive properties, but no cells that will bring the fusion together. Mesenchymal stem cells (MSCs) harvested from the bone marrow, adipose tissue, periosteum or skeletal muscle have been confirmed to differentiate into osteoblasts both *in vitro* and *in vivo*[12-17]. Adipose derived stem cells (ADSCs) harvested from fat pads, although less commonly utilized in experimental models, are multipotent cells that can differentiate into adipocytes, osteoblasts, chondrocytes, or myocytes when cultivated in the correct microenvironment[17-21]. Both types of cells have been demonstrated to have a significant effect on spinal fusion in a multitude of settings including a variety of culturing mechanisms, scaffolds and added growth factors. Bone morphogenetic protein-2 (BMP-2) is a growth factor which is increasingly used in spinal fusion, mostly on an off-label basis, which may be the reason for the increased incidence of complications associated with its utilization[22]. Genetically modified MSCs which were induced to express BMP-2 were reported to induce spinal fusion in mice after injection into the paraspinal musculature comparable, in terms of rigidity, to the fusion achieved with instrumentation[23,24]. Fu *et al*[25] addressed the concern of complications associated with BMP-2 by examining if a reduced amount combined with MSCs would still yield acceptable fusion rates. They found that the group with MSCs seeded on alginate with a low dose of BMP-2 achieved equal fusion rates to the group treated with an iliac crest autograft in a rabbit model[25]. Additional evidence that MSCs may potentially serve as a substitute for autograft or BMP-2 has been presented, however, slightly lower fusion rates were reported for the group treated with MSCs *vs* the group treated with BMP-2 in a rabbit model[26]. Seo *et al*[27] attempted to induce higher fusion rates in a rat model by transplanting MSCs seeded on hydroxyapatite in addition to fibroblast growth factor-4, but found that the group treated without the addition of the growth factor achieved the highest fusion rate[27]. Other than selection of the appropriate growth factor, the level of osteogenic differentiation of the cells may also play a role. One study reported that 80% of rabbit spines treated with MSCs cultured in osteogenic differentiation medium fused *vs* only 33.3% of spines treated with cells that had been cultured without

the addition of differentiation medium[28]. The efficacy of MSCs transplanted without amendments to culturing protocols, the addition of genetic engineering or growth factors has been less encouraging in a variety of animal models utilizing beta-tricalcium phosphate graft or porous ceramics[29-31]. Recently, stem cells derived from adipose tissue have become popular in the tissue engineering community, in part due to the ease of cell harvesting from fat pads through liposuction. ADSCs expressing bone morphogenic proteins have proven effective for spinal fusion in animal models of metabolic bone disease[32,33]. In a study comparing MSCs and ADSCs expressing BMP-2 seeded on collagen sponges, fusion rates were encouraging and not significantly different in the two groups of rat models[34]. Due to the relatively easier clinical access to ADSCs in the patient, greater attention to their potential role in spinal fusion is warranted. Overall, the use of stem cells in clinical spine fusion has been restricted due to the limited number of cells which may be harvested through liposuction or bone marrow puncture. Cellular *in vitro* expansion is necessary to increase the number of viable pluripotent cells. This represents the greatest burden in the bench to bedside translation of stem cells in spine fusion, as two separate procedures, the availability of sophisticated instrumentation and educated personnel decrease the cost-effectiveness of the intervention[35-37].

Disc regeneration

Degenerative Disk Disease results from a complex process regulated by biomechanical forces and molecular changes within the disk. A healthy disk consists of the nucleus pulposus rich in collagen type Ⅱ fibers with a high content of proteoglycan and aggrecan to aid in the resistance to compression[38,39]. It is surrounded by the annulus fibrosus, rich in collagen type Ⅰ fibers which are arranged in a parallel fashion to withstand bending and twisting forces. A healthy disk is aneural and avascular due to the high proteoglycan content of the nucleus pulposus, receiving most of its nutrients by diffusion through the vertebral endplate[40]. Starting at the second decade of life, the progressive calcification of the endplate results in a decrease in the nutrient supply to the disk[41]. This has been hypothesized to result in phenotypic changes leading to decreased synthesis of proteoglycan and collagen type Ⅱ, and increased synthesis of collagen type Ⅰ and Ⅲ as well as an increase in matrix metalloproteinase activity[41-44]. Overall, the change in the biochemical composition of the disk results in gross morphologic changes and decreased disk height which contribute to the impingement of nerves[45-47]. The clinical manifestation of Degenerative Disk Disease in the form of lower back pain is usually focused on conservative management including lifestyle- or work modifications, physical therapy, pain medication, acupuncture and epidural injections. If the symptoms are persistent, cause progressive deformity or neurologic compromise, surgery in the form of disc replacement or spinal fusion is considered[48]. Growth factors, inflammatory cytokine antagonists and intracellular regulatory proteins are among the factors which have been demonstrated to result in encouraging regeneration of nucleus pulposus cells *in vitro* and *in vivo*[49-53]. The utility of these therapies in humans may be limited due to the rapid *in vivo* degeneration of the molecules used for the treatment. Gene therapy, although successfully utilized in animal studies, has significant risks concerning the vectors used for gene transduction. Stem cell therapy for Degenerative Disk Disease is based on the premise of reconstruction of the nucleus pulposus matrix. Nishimura and Mochida were the first to reimplant autologous nucleus pulposus cells in a disk herniation rat model and reported decreased degeneration of the annulus fibrosus, the endplate and the remaining nucleus pulposus when compared to the control group[54]. As with bony fusion, most scientists have focused on MSCs for Degenerative Disk regeneration. MSCs can differentiate into cell lineages populating bone, cartilage, skeletal muscle and ligamentous tissue[15]. As the exact phenotype of nucleus pulposus cells has yet to be determined, confirmation of the possibility of MSCs to differentiate into nucleus pulposus cells capable of proteoglycan production does not exist. Nonetheless, researchers have demonstrated that various environmental stimuli and genetic manipulations may result in an MSC differentiating into a nucleus pulposus-like cell. Richardson *et al*[55] transfected MSCs using the transcription factor, SOX-9, and found that they differentiated into chondrocyte-like cells with the deposition of nucleus pulposus matrix markers collagen type Ⅱ and aggrecan[55]. Risbud *et al*[56,57] experimentally cultured immobilized MSCs under hypoxic conditions with transforming growth factor-beta and found that these conditions prompted MSC differentiation towards nucleus pulposus-like cells[56,57]. Similar differentiation of stem cells into cells which expressed nucleus pulposus-like phenotypic markers has been observed in rabbit studies. Sakai *et al*[58,59] studied the effect of the transplantation of MSCs into both healthy and degenerated disks. They found that the implanted cells differentiated into nucleus pulposus-like cells, producing collagen type Ⅱ and proteoglycan without harm to the rabbit[58,59]. The degenerated disks showed significant improvement in height and hydration[60]. Allogenic MSCs were transplanted into the intervertebral disk in a rat model, and demonstrated viability and proliferation[61]. However, concerns regarding an immune reaction to allogenic stem cells in humans have limited the utilization of such cells in clinical trials. Orozco *et al*[62] transplanted autologous MSCs into ten patients diagnosed with Degenerative Disk Disease[62]. They found improvements in pain and disability within three months of treatment. Their study had severe limitations regarding the average age of the patients (35 years) and the number of patients (10). Nonetheless, these results exemplify the importance of arranging larger clinical trials to ease the translation of stem cell therapy from bench to bedside for patients suffering from Degenerative Disk Disease.

Spinal cord injury

Spinal cord injury (SCI) results from traumatic damage to the spinal cord which may have devastating consequences

or result in death[63]. The most common causes of traumatic SCI are motor vehicle accidents, sports injuries, falls at home, and traumatic injury in the workplace[64]. A total of 15-40 cases per million people are estimated to suffer a SCI every year, with most cases occurring in males 16-30 years of age[65-67]. SCI consists of several complex phases which are yet to be elucidated fully on a molecular level. The primary or acute phase consists of the physical disruption and contusion of the nerves and the tissues surrounding the spinal cord[68]. The force of the traumatic disturbance correlates directly with the amount of cell death[69]. As a consequence, the spinal cord swells and concomitantly with the commonly associated hemorrhage impedes blood flow, causing hypoxia[70-74]. The second or sub-acute phase of SCI is characterized by overlapping phases of sustained inflammation, oxidative and immune events. Excessive glutamate levels, the formation of reactive oxygen species and lipid peroxidation cause widespread neuronal and glial death, and axonal degeneration[75-79]. The scar tissue which is generated during the third or chronic phase presents a physical and biochemical barrier for axonal regeneration, complicating recovery[80,81]. Scientists have experimented with stem cell transplantation in the hope of promoting functional recovery after SCI. The intervention may be targeted at different phases, but should ideally enhance neuron and axon regeneration and remyelination through the creation of a favorable microenvironment or the direct physical replacement of cells[82]. This may best be achieved through suppression of the inflammatory cascade resulting in cell apoptosis and necrosis[83]. Embryonic stem cells, pluripotent cells derived from the inner cell mass of an embryo, have been considered as a treatment option for SCI[84]. Although these cells can divide infinitely and have greater differentiation potential than adult stem cells, their use is highly controversial[85-89]. A Chinese surgeon who claimed to have cured SCI in hundreds of patients without complications by injecting them with olfactory ensheathing cells isolated from aborted fetuses was received with great skepticism and sparked fierce debates about the ethicality of such research[90-93]. The Gevron Corporation is the first company to have received approval to initiate a clinical trial assessing a human embryonic stem cell-derived candidate therapy for severe spinal cord injuries in the United States[94]. Adult stem cells have more commonly been used in both *in vitro* and *in vivo* experimentation due to the ethical concerns regarding embryonic stem cells. MSCs are favored by many scientists due to the ease of cell harvest, isolation, expansion, and preservation[35,95-97]. To date, no reports of immunologic reactions to allogeneic *vs* autologous cell transplants have been observed, making MSCs a very practical solution for cellular therapy[98,99]. MSCs have been demonstrated to promote axonal regeneration and suppress demyelination[100]. Several different studies in rat models found that MSCs induce nerve regeneration, modulate the production of inflammatory cytokines such as TNF-α and IL-6 and reduce myeloperoxidase activity[101-105]. Menezes *et al*[106] hypothesized that laminin may play a pivotal role in neuron and axon preservation and regeneration after finding deposits of the glycoprotein on the lesion site in a rat SCI model[106]. All of these studies reported that transplanted MSCs operate mainly through the creation of a favorable microenvironment by means of the secretion of a variety of neurotrophic factors[107-111]. However, the *in vivo* differentiation of MSCs into neuron-like cells has been documented to be inefficient[108-110]. Therefore, MSCs are as of now, not capable of directly repopulating and physically restoring the damaged tissue in SCI. Neural stem cells (NSCs) were sought as an option for stem cell therapy, specifically for their ability to overcome this deficit. NSCs are harvested from the subventricular zone and are capable of differentiation into neurons, oligodendrocytes and most commonly astrocytes[112,113]. Nemati *et al*[114] reported that the transplantation of NSCs into a contusion SCI in a monkey model facilitated hind limb performance recovery[114]. Lee *et al*[115] documented similar functional recovery in terms of hind limb recovery paired with reduced lesions and an increased density of axons and dendritic spines surrounding the transplanted NSCs in a rat model[115]. Piltti *et al*[116] examined the survival rates, migration and sensory fiber sprouting of transplanted NSCs in a rat model in the secondary or subacute phase *vs* the tertiary or chronic phase of SCI. They found that the number of surviving transplanted cells was lower in the group treated during the tertiary phase, but that these cells had a stronger effect by increasing the number of mature oligodendrocytes[116]. The experimental utilization of stem cell therapy in SCI has been very limited to date. Several studies have reported sensory and motor improvements after 1-3 mo of stem cell transplantations combined with various other cells and growth factors[117-121]. In contrast, Karamouzian *et al*[122] stated that despite the feasibility and safety of cellular transplantations, the improvements in terms of functional recovery were not statistically significant in their study[122]. The low numbers of patients in these studies make it difficult to provide a definitive statement on the clinical potential of stem cell transplantation for SCI.

CONCLUSION

Additional areas of interest which have not been clinically addressed with stem cell therapy are iatrogenic nerve and muscle injury caused by spinal surgery. Additional considerations are warranted with respect to the ethics and the cancerogenous risk of embryonic stem cell therapy, the potential immune reaction to autologous cell transplantation as well as the clinical morbidity of adult stem cell harvest. Overall, greater standardization of *in vitro* experimentation and animal models may aid the speed of translation of stem cell therapy in spinal surgery from bench to bedside.

REFERENCES

1 **Deyo RA**, Gray DT, Kreuter W, Mirza S, Martin BI. United States trends in lumbar fusion surgery for degenerative conditions. *Spine* (Phila Pa 1976) 2005; **30**: 1441-1445; discussion 1446-1447 [PMID: 15959375]
2 **Gray DT**, Deyo RA, Kreuter W, Mirza SK, Heagerty PJ,

Comstock BA, Chan L. Population-based trends in volumes and rates of ambulatory lumbar spine surgery. *Spine* (Phila Pa 1976) 2006; **31**: 1957-1963; discussion 1964 [PMID: 16924213]
3 **Cowan JA**, Dimick JB, Wainess R, Upchurch GR, Chandler WF, La Marca F. Changes in the utilization of spinal fusion in the United States. *Neurosurgery* 2006; **59**: 15-20; discussion 15-20 [PMID: 16823295 DOI: 10.1227/01.NEU.0000219836.54861.CD]
4 **Martin BI**, Mirza SK, Comstock BA, Gray DT, Kreuter W, Deyo RA. Are lumbar spine reoperation rates falling with greater use of fusion surgery and new surgical technology? *Spine* (Phila Pa 1976) 2007; **32**: 2119-2126 [PMID: 17762814]
5 **Mok JM**, Cloyd JM, Bradford DS, Hu SS, Deviren V, Smith JA, Tay B, Berven SH. Reoperation after primary fusion for adult spinal deformity: rate, reason, and timing. *Spine* (Phila Pa 1976) 2009; **34**: 832-839 [PMID: 19365253 DOI: 10.1097/BRS.0b013e31819f2080]
6 **Kim YJ**, Bridwell KH, Lenke LG, Rhim S, Cheh G. Pseudarthrosis in long adult spinal deformity instrumentation and fusion to the sacrum: prevalence and risk factor analysis of 144 cases. *Spine* (Phila Pa 1976) 2006; **31**: 2329-2336 [PMID: 16985461]
7 **Pichelmann MA**, Lenke LG, Bridwell KH, Good CR, O'Leary PT, Sides BA. Revision rates following primary adult spinal deformity surgery: six hundred forty-three consecutive patients followed-up to twenty-two years postoperative. *Spine* (Phila Pa 1976) 2010; **35**: 219-226 [PMID: 20038867 DOI: 10.1097/BRS.0b013e3181c91180]
8 **Kim YJ**, Bridwell KH, Lenke LG, Rinella AS, Edwards C. Pseudarthrosis in primary fusions for adult idiopathic scoliosis: incidence, risk factors, and outcome analysis. *Spine* (Phila Pa 1976) 2005; **30**: 468-474 [PMID: 15706346]
9 **Cavagna R**, Tournier C, Aunoble S, Bouler JM, Antonietti P, Ronai M, Le Huec JC. Lumbar decompression and fusion in elderly osteoporotic patients: a prospective study using less rigid titanium rod fixation. *J Spinal Disord Tech* 2008; **21**: 86-91 [PMID: 18391710 DOI: 10.1097/BSD.0b013e3180590c23]
10 **Hart RA**, Prendergast MA. Spine surgery for lumbar degenerative disease in elderly and osteoporotic patients. *Instr Course Lect* 2007; **56**: 257-272 [PMID: 17472312]
11 **Keaveny TM**, Yeh OC. Architecture and trabecular bone - toward an improved understanding of the biomechanical effects of age, sex and osteoporosis. *J Musculoskelet Neuronal Interact* 2002; **2**: 205-208 [PMID: 15758434]
12 **Caplan AI**, Bruder SP. Mesenchymal stem cells: building blocks for molecular medicine in the 21st century. *Trends Mol Med* 2001; **7**: 259-264 [PMID: 11378515 DOI: 10.1016/S1471-4914(01)02016-0]
13 **Alhadlaq A**, Mao JJ. Mesenchymal stem cells: isolation and therapeutics. *Stem Cells Dev* 2004; **13**: 436-448 [PMID: 15345137 DOI: 10.1089/scd.2004.13.436]
14 **Mauney JR**, Kirker-Head C, Abrahamson L, Gronowicz G, Volloch V, Kaplan DL. Matrix-mediated retention of in vitro osteogenic differentiation potential and in vivo bone-forming capacity by human adult bone marrow-derived mesenchymal stem cells during ex vivo expansion. *J Biomed Mater Res A* 2006; **79**: 464-475 [PMID: 16752403 DOI: 10.1002/jbm.a.30876]
15 **Williams JT**, Southerland SS, Souza J, Calcutt AF, Cartledge RG. Cells isolated from adult human skeletal muscle capable of differentiating into multiple mesodermal phenotypes. *Am Surg* 1999; **65**: 22-26 [PMID: 9915526]
16 **Nakahara H**, Dennis JE, Bruder SP, Haynesworth SE, Lennon DP, Caplan AI. In vitro differentiation of bone and hypertrophic cartilage from periosteal-derived cells. *Exp Cell Res* 1991; **195**: 492-503 [PMID: 2070830 DOI: 10.1016/0014-4827(91)90401-F]
17 **Zuk PA**, Zhu M, Mizuno H, Huang J, Futrell JW, Katz AJ, Benhaim P, Lorenz HP, Hedrick MH. Multilineage cells from human adipose tissue: implications for cell-based therapies. *Tissue Eng* 2001; **7**: 211-228 [PMID: 11304456 DOI: 10.1089/107632701300062859]
18 **Fraser JK**, Wulur I, Alfonso Z, Hedrick MH. Fat tissue: an underappreciated source of stem cells for biotechnology. *Trends Biotechnol* 2006; **24**: 150-154 [PMID: 16488036 DOI: 10.1016/j.tibtech.2006.01.010]
19 **Erickson GR**, Gimble JM, Franklin DM, Rice HE, Awad H, Guilak F. Chondrogenic potential of adipose tissue-derived stromal cells in vitro and in vivo. *Biochem Biophys Res Commun* 2002; **290**: 763-769 [PMID: 11785965 DOI: 10.1006/bbrc.2001.6270]
20 **Lee SJ**, Kang SW, Do HJ, Han I, Shin DA, Kim JH, Lee SH. Enhancement of bone regeneration by gene delivery of BMP2/Runx2 bicistronic vector into adipose-derived stromal cells. *Biomaterials* 2010; **31**: 5652-5659 [PMID: 20413153 DOI: 10.1016/j.biomaterials.2010.03.019]
21 **Weinzierl K**, Hemprich A, Frerich B. Bone engineering with adipose tissue derived stromal cells. *J Craniomaxillofac Surg* 2006; **34**: 466-471 [PMID: 17157521 DOI: 10.1016/j.jcms.2006.07.860]
22 **Carragee EJ**, Baker RM, Benzel EC, Bigos SJ, Cheng I, Corbin TP, Deyo RA, Hurwitz EL, Jarvik JG, Kang JD, Lurie JD, Mroz TE, Oner FC, Peul WC, Rainville J, Ratliff JK, Rihn JA, Rothman DJ, Schoene ML, Spengler DM, Weiner BK. A biologic without guidelines: the YODA project and the future of bone morphogenetic protein-2 research. *Spine J* 2012; **12**: 877-880 [PMID: 23199819 DOI: 10.1016/j.spinee.2012.11.002]
23 **Hasharoni A**, Zilberman Y, Turgeman G, Helm GA, Liebergall M, Gazit D. Murine spinal fusion induced by engineered mesenchymal stem cells that conditionally express bone morphogenetic protein-2. *J Neurosurg Spine* 2005; **3**: 47-52 [PMID: 16122022 DOI: 10.3171/spi.2005.3.1.0047]
24 **Sheyn D**, Rüthemann M, Mizrahi O, Kallai I, Zilberman Y, Tawackoli W, Kanim LE, Zhao L, Bae H, Pelled G, Snedeker JG, Gazit D. Genetically modified mesenchymal stem cells induce mechanically stable posterior spine fusion. *Tissue Eng Part A* 2010; **16**: 3679-3686 [PMID: 20618082 DOI: 10.1089/ten.tea.2009.0786]
25 **Fu TS**, Chen WJ, Chen LH, Lin SS, Liu SJ, Ueng SW. Enhancement of posterolateral lumbar spine fusion using low-dose rhBMP-2 and cultured marrow stromal cells. *J Orthop Res* 2009; **27**: 380-384 [PMID: 18853429 DOI: 10.1002/jor.20644]
26 **Minamide A**, Yoshida M, Kawakami M, Yamasaki S, Kojima H, Hashizume H, Boden SD. The use of cultured bone marrow cells in type I collagen gel and porous hydroxyapatite for posterolateral lumbar spine fusion. *Spine* (Phila Pa 1976) 2005; **30**: 1134-1138 [PMID: 15897826]
27 **Seo HS**, Jung JK, Lim MH, Hyun DK, Oh NS, Yoon SH. Evaluation of Spinal Fusion Using Bone Marrow Derived Mesenchymal Stem Cells with or without Fibroblast Growth Factor-4. *J Korean Neurosurg Soc* 2009; **46**: 397-402 [PMID: 19893733 DOI: 10.3340/jkns.2009.46.4.397]
28 **Nakajima T**, Iizuka H, Tsutsumi S, Kayakabe M, Takagishi K. Evaluation of posterolateral spinal fusion using mesenchymal stem cells: differences with or without osteogenic differentiation. *Spine* (Phila Pa 1976) 2007; **32**: 2432-2436 [PMID: 18090081]
29 **Gupta MC**, Theerajunyaporn T, Maitra S, Schmidt MB, Holy CE, Kadiyala S, Bruder SP. Efficacy of mesenchymal stem cell enriched grafts in an ovine posterolateral lumbar spine model. *Spine* (Phila Pa 1976) 2007; **32**: 720-726; discussion 727 [PMID: 17414903]
30 **Orii H**, Sotome S, Chen J, Wang J, Shinomiya K. Beta-tricalcium phosphate (beta-TCP) graft combined with bone marrow stromal cells (MSCs) for posterolateral spine fusion. *J Med Dent Sci* 2005; **52**: 51-57 [PMID: 15868741]
31 **Cinotti G**, Patti AM, Vulcano A, Della Rocca C, Polveroni G, Giannicola G, Postacchini F. Experimental posterolateral

spinal fusion with porous ceramics and mesenchymal stem cells. *J Bone Joint Surg Br* 2004; **86**: 135-142 [PMID: 14765881]
32 **Hsu WK**, Wang JC, Liu NQ, Krenek L, Zuk PA, Hedrick MH, Benhaim P, Lieberman JR. Stem cells from human fat as cellular delivery vehicles in an athymic rat posterolateral spine fusion model. *J Bone Joint Surg Am* 2008; **90**: 1043-1052 [PMID: 18451397 DOI: 10.2106/JBJS.G.00292]
33 **Sheyn D**, Kallai I, Tawackoli W, Cohn Yakubovich D, Oh A, Su S, Da X, Lavi A, Kimelman-Bleich N, Zilberman Y, Li N, Bae H, Gazit Z, Pelled G, Gazit D. Gene-modified adult stem cells regenerate vertebral bone defect in a rat model. *Mol Pharm* 2011; **8**: 1592-1601 [PMID: 21834548 DOI: 10.1021/mp200226c]
34 **Miyazaki M**, Zuk PA, Zou J, Yoon SH, Wei F, Morishita Y, Sintuu C, Wang JC. Comparison of human mesenchymal stem cells derived from adipose tissue and bone marrow for ex vivo gene therapy in rat spinal fusion model. *Spine* (Phila Pa 1976) 2008; **33**: 863-869 [PMID: 18404105 DOI: 10.1097/BRS.0b013e31816b45c3]
35 **Kotobuki N**, Hirose M, Takakura Y, Ohgushi H. Cultured autologous human cells for hard tissue regeneration: preparation and characterization of mesenchymal stem cells from bone marrow. *Artif Organs* 2004; **28**: 33-39 [PMID: 14720286 DOI: 10.1111/j.1525-1594.2004.07320.x]
36 **Ohgushi H**, Kitamura S, Kotobuki N, Hirose M, Machida H, Muraki K, Takakura Y. Clinical application of marrow mesenchymal stem cells for hard tissue repair. *Yonsei Med J* 2004; **45** Suppl: 61-67 [PMID: 15250053 DOI: 10.3349/ymj.2004.45.Suppl.61]
37 **Bruder SP**, Jaiswal N, Ricalton NS, Mosca JD, Kraus KH, Kadiyala S. Mesenchymal stem cells in osteobiology and applied bone regeneration. *Clin Orthop Relat Res* 1998; **(355 Suppl)**: S247-S256 [PMID: 9917644 DOI: 10.1097/00003086-199810001-00025]
38 **Kepler CK**, Anderson DG, Tannoury C, Ponnappan RK. Intervertebral disk degeneration and emerging biologic treatments. *J Am Acad Orthop Surg* 2011; **19**: 543-553 [PMID: 21885700]
39 **Roberts S**, Evans H, Trivedi J, Menage J. Histology and pathology of the human intervertebral disc. *J Bone Joint Surg Am* 2006; **88** Suppl 2: 10-14 [PMID: 16595436 DOI: 10.2106/JBJS.F.00019]
40 **Johnson WE**, Caterson B, Eisenstein SM, Hynds DL, Snow DM, Roberts S. Human intervertebral disc aggrecan inhibits nerve growth in vitro. *Arthritis Rheum* 2002; **46**: 2658-2664 [PMID: 12384924 DOI: 10.1002/art.10585]
41 **Antoniou J**, Steffen T, Nelson F, Winterbottom N, Hollander AP, Poole RA, Aebi M, Alini M. The human lumbar intervertebral disc: evidence for changes in the biosynthesis and denaturation of the extracellular matrix with growth, maturation, ageing, and degeneration. *J Clin Invest* 1996; **98**: 996-1003 [PMID: 8770872 DOI: 10.1172/JCI118884]
42 **Roughley PJ**. Biology of intervertebral disc aging and degeneration: involvement of the extracellular matrix. *Spine* (Phila Pa 1976) 2004; **29**: 2691-2699 [PMID: 15564918]
43 **Chan WC**, Sze KL, Samartzis D, Leung VY, Chan D. Structure and biology of the intervertebral disk in health and disease. *Orthop Clin North Am* 2011; **42**: 447-464, vii [PMID: 21944583 DOI: 10.1016/j.ocl.2011.07.012]
44 **Urban JP**, Roberts S. Degeneration of the intervertebral disc. *Arthritis Res Ther* 2003; **5**: 120-130 [PMID: 12723977 DOI: 10.1186/ar629]
45 **Nerlich AG**, Schleicher ED, Boos N. 1997 Volvo Award winner in basic science studies. Immunohistologic markers for age-related changes of human lumbar intervertebral discs. *Spine* (Phila Pa 1976) 1997; **22**: 2781-2795 [PMID: 9431614]
46 **Siemionow K**, An H, Masuda K, Andersson G, Cs-Szabo G. The effects of age, sex, ethnicity, and spinal level on the rate of intervertebral disc degeneration: a review of 1712 intervertebral discs. *Spine* (Phila Pa 1976) 2011; **36**: 1333-1339 [PMID: 21217432 DOI: 10.1097/BRS.0b013e3181f2a177]
47 **Weiler C**, Schietzsch M, Kirchner T, Nerlich AG, Boos N, Wuertz K. Age-related changes in human cervical, thoracal and lumbar intervertebral disc exhibit a strong intra-individual correlation. *Eur Spine J* 2012; **21** Suppl 6: S810-S818 [PMID: 21837413 DOI: 10.1007/s00586-011-1922-3]
48 **Madigan L**, Vaccaro AR, Spector LR, Milam RA. Management of symptomatic lumbar degenerative disk disease. *J Am Acad Orthop Surg* 2009; **17**: 102-111 [PMID: 19202123]
49 **Thompson JP**, Oegema TR, Bradford DS. Stimulation of mature canine intervertebral disc by growth factors. *Spine* (Phila Pa 1976) 1991; **16**: 253-260 [PMID: 2028297]
50 **Okuda S**, Myoui A, Ariga K, Nakase T, Yonenobu K, Yoshikawa H. Mechanisms of age-related decline in insulin-like growth factor-I dependent proteoglycan synthesis in rat intervertebral disc cells. *Spine* (Phila Pa 1976) 2001; **26**: 2421-2426 [PMID: 11707703]
51 **Takegami K**, Thonar EJ, An HS, Kamada H, Masuda K. Osteogenic protein-1 enhances matrix replenishment by intervertebral disc cells previously exposed to interleukin-1. *Spine* (Phila Pa 1976) 2002; **27**: 1318-1325 [PMID: 12065981]
52 **Li J**, Kim KS, Park JS, Elmer WA, Hutton WC, Yoon ST. BMP-2 and CDMP-2: stimulation of chondrocyte production of proteoglycan. *J Orthop Sci* 2003; **8**: 829-835 [PMID: 14648273 DOI: 10.1007/s00776-003-0719-6]
53 **Roberts S**, Evans H, Menage J, Urban JP, Bayliss MT, Eisenstein SM, Rugg MS, Milner CM, Griffin S, Day AJ. TNFalpha-stimulated gene product (TSG-6) and its binding protein, IalphaI, in the human intervertebral disc: new molecules for the disc. *Eur Spine J* 2005; **14**: 36-42 [PMID: 15549486 DOI: 10.1007/s00586-004-0798-x]
54 **Nishimura K**, Mochida J. Percutaneous reinsertion of the nucleus pulposus. An experimental study. *Spine* (Phila Pa 1976) 1998; **23**: 1531-1538; discussion 1539 [PMID: 9682309]
55 **Richardson SM**, Curran JM, Chen R, Vaughan-Thomas A, Hunt JA, Freemont AJ, Hoyland JA. The differentiation of bone marrow mesenchymal stem cells into chondrocyte-like cells on poly-L-lactic acid (PLLA) scaffolds. *Biomaterials* 2006; **27**: 4069-4078 [PMID: 16569429 DOI: 10.1016/j.biomaterials.2006.03.017]
56 **Risbud MV**, Albert TJ, Guttapalli A, Vresilovic EJ, Hillibrand AS, Vaccaro AR, Shapiro IM. Differentiation of mesenchymal stem cells towards a nucleus pulposus-like phenotype in vitro: implications for cell-based transplantation therapy. *Spine* (Phila Pa 1976) 2004; **29**: 2627-2632 [PMID: 15564911]
57 **Risbud MV**, Guttapalli A, Albert TJ, Shapiro IM. Hypoxia activates MAPK activity in rat nucleus pulposus cells: regulation of integrin expression and cell survival. *Spine* (Phila Pa 1976) 2005; **30**: 2503-2509 [PMID: 16284587]
58 **Sakai D**, Mochida J, Yamamoto Y, Nomura T, Okuma M, Nishimura K, Nakai T, Ando K, Hotta T. Transplantation of mesenchymal stem cells embedded in Atelocollagen gel to the intervertebral disc: a potential therapeutic model for disc degeneration. *Biomaterials* 2003; **24**: 3531-3541 [PMID: 12809782 DOI: 10.1016/S0142-9612(03)00222-9]
59 **Sakai D**, Mochida J, Iwashina T, Hiyama A, Omi H, Imai M, Nakai T, Ando K, Hotta T. Regenerative effects of transplanting mesenchymal stem cells embedded in atelocollagen to the degenerated intervertebral disc. *Biomaterials* 2006; **27**: 335-345 [PMID: 16112726 DOI: 10.1016/j.biomaterials.2005.06.038]
60 **Sakai D**, Mochida J, Iwashina T, Watanabe T, Nakai T, Ando K, Hotta T. Differentiation of mesenchymal stem cells transplanted to a rabbit degenerative disc model: potential and limitations for stem cell therapy in disc regeneration. *Spine* (Phila Pa 1976) 2005; **30**: 2379-2387 [PMID: 16261113]
61 **Crevensten G**, Walsh AJ, Ananthakrishnan D, Page P, Wahba GM, Lotz JC, Berven S. Intervertebral disc cell therapy for regeneration: mesenchymal stem cell implantation in rat intervertebral discs. *Ann Biomed Eng* 2004; **32**: 430-434 [PMID:

15095817 DOI: 10.1023/B: ABME.0000017545.84833.7c]
62 **Orozco L**, Soler R, Morera C, Alberca M, Sánchez A, García-Sancho J. Intervertebral disc repair by autologous mesenchymal bone marrow cells: a pilot study. *Transplantation* 2011; **92**: 822-828 [PMID: 21792091 DOI: 10.1097/TP.0b013e3182298a15]
63 **Yip PK**, Malaspina A. Spinal cord trauma and the molecular point of no return. *Mol Neurodegener* 2012; **7**: 6 [PMID: 22315999 DOI: 10.1186/1750-1326-7-6]
64 **Tator CH**. Contemporary Management Of Spinal Cord Injury. Epidemiology and general characteristics of the spinal cord injury patient. In: Benzel EC, editor. Park Ridge, Illinois, USA: American Association of Neurological Surgeons, 1995: 9-13
65 **Ackery A**, Tator C, Krassioukov A. A global perspective on spinal cord injury epidemiology. *J Neurotrauma* 2004; **21**: 1355-1370 [PMID: 15672627 DOI: 10.1089/neu.2004.21.1355]
66 **Wyndaele M**, Wyndaele JJ. Incidence, prevalence and epidemiology of spinal cord injury: what learns a worldwide literature survey? *Spinal Cord* 2006; **44**: 523-529 [PMID: 16389270 DOI: 10.1038/sj.sc.3101893]
67 **Noonan VK**, Fingas M, Farry A, Baxter D, Singh A, Fehlings MG, Dvorak MF. Incidence and prevalence of spinal cord injury in Canada: a national perspective. *Neuroepidemiology* 2012; **38**: 219-226 [PMID: 22555590 DOI: 10.1159/000336014]
68 **Sekhon LH**, Fehlings MG. Epidemiology, demographics, and pathophysiology of acute spinal cord injury. *Spine* (Phila Pa 1976) 2001; **26**: S2-12 [PMID: 11805601]
69 **Fehlings MG**, Tator CH. The relationships among the severity of spinal cord injury, residual neurological function, axon counts, and counts of retrogradely labeled neurons after experimental spinal cord injury. *Exp Neurol* 1995; **132**: 220-228 [PMID: 7789460 DOI: 10.1016/0014-4886(95)90027-6]
70 **Bramlett HM**, Dietrich WD. Progressive damage after brain and spinal cord injury: pathomechanisms and treatment strategies. *Prog Brain Res* 2007; **161**: 125-141 [PMID: 17618974 DOI: 10.1016/S0079-6123(06)61009-1]
71 **Bullock R**, Maxwell WL, Graham DI, Teasdale GM, Adams JH. Glial swelling following human cerebral contusion: an ultrastructural study. *J Neurol Neurosurg Psychiatry* 1991; **54**: 427-434 [PMID: 1865206 DOI: 10.1136/jnnp.54.5.427]
72 **Donnelly DJ**, Popovich PG. Inflammation and its role in neuroprotection, axonal regeneration and functional recovery after spinal cord injury. *Exp Neurol* 2008; **209**: 378-388 [PMID: 17662717 DOI: 10.1016/j.expneurol.2007.06.009]
73 **Kwon BK**, Hillyer J, Tetzlaff W. Translational research in spinal cord injury: a survey of opinion from the SCI community. *J Neurotrauma* 2010; **27**: 21-33 [PMID: 19751098 DOI: 10.1089/neu.2009.1048]
74 **Profyris C**, Cheema SS, Zang D, Azari MF, Boyle K, Petratos S. Degenerative and regenerative mechanisms governing spinal cord injury. *Neurobiol Dis* 2004; **15**: 415-436 [PMID: 15056450 DOI: 10.1016/j.nbd.2003.11.015]
75 **Carlson SL**, Parrish ME, Springer JE, Doty K, Dossett L. Acute inflammatory response in spinal cord following impact injury. *Exp Neurol* 1998; **151**: 77-88 [PMID: 9582256 DOI: 10.1006/exnr.1998.6785]
76 **Keane RW**, Davis AR, Dietrich WD. Inflammatory and apoptotic signaling after spinal cord injury. *J Neurotrauma* 2006; **23**: 335-344 [PMID: 16629620 DOI: 10.1089/neu.2006.23.335]
77 **Liu XZ**, Xu XM, Hu R, Du C, Zhang SX, McDonald JW, Dong HX, Wu YJ, Fan GS, Jacquin MF, Hsu CY, Choi DW. Neuronal and glial apoptosis after traumatic spinal cord injury. *J Neurosci* 1997; **17**: 5395-5406 [PMID: 9204923]
78 **Taoka Y**, Okajima K, Uchiba M, Murakami K, Kushimoto S, Johno M, Naruo M, Okabe H, Takatsuki K. Role of neutrophils in spinal cord injury in the rat. *Neuroscience* 1997; **79**: 1177-1182 [PMID: 9219976 DOI: 10.1016/S0306-4522(97)00011-0]
79 **Wang JT**, Medress ZA, Barres BA. Axon degeneration: molecular mechanisms of a self-destruction pathway. *J Cell Biol* 2012; **196**: 7-18 [PMID: 22232700 DOI: 10.1083/jcb.201108111]
80 **Fawcett JW**, Asher RA. The glial scar and central nervous system repair. *Brain Res Bull* 1999; **49**: 377-391 [PMID: 10483914 DOI: 10.1016/S0361-9230(99)00072-6]
81 **Rudge JS**, Silver J. Inhibition of neurite outgrowth on astroglial scars in vitro. *J Neurosci* 1990; **10**: 3594-3603 [PMID: 2230948]
82 **Pearse DD**, Bunge MB. Designing cell- and gene-based regeneration strategies to repair the injured spinal cord. *J Neurotrauma* 2006; **23**: 438-452 [PMID: 16629628 DOI: 10.1089/neu.2006.23.437]
83 **Garbossa D**, Boido M, Fontanella M, Fronda C, Ducati A, Vercelli A. Recent therapeutic strategies for spinal cord injury treatment: possible role of stem cells. *Neurosurg Rev* 2012; **35**: 293-311; discussion 311 [PMID: 22539011 DOI: 10.1007/s10143-012-0385-2]
84 **Blair K**, Wray J, Smith A. The liberation of embryonic stem cells. *PLoS Genet* 2011; **7**: e1002019 [PMID: 21490948 DOI: 10.1371/journal.pgen.1002019]
85 **Shand J**, Berg J, Bogue C. Human embryonic stem cell (hESC) and human embryo research. *Pediatrics* 2012; **130**: 972-977 [PMID: 23109685 DOI: 10.1542/peds.2012-2482]
86 **Spiegel AM**. The stem cell wars: a dispatch from the front. *Trans Am Clin Climatol Assoc* 2013; **124**: 94-110 [PMID: 23874014]
87 **Pera M**, Trounson A. Cloning debate: Stem-cell researchers must stay engaged. *Nature* 2013; **498**: 159-161 [PMID: 23765475 DOI: 10.1038/498159a]
88 **Critchley CR**, Bruce G, Farrugia M. The impact of commercialisation on public perceptions of stem cell research: exploring differences across the use of induced pluripotent cells, human and animal embryos. *Stem Cell Rev* 2013; **9**: 541-554 [PMID: 23695820 DOI: 10.1007/s12015-013-9445-4]
89 **Ethics Committee of American Society for Reproductive Medicine.** Donating embryos for human embryonic stem cell (hESC) research: a committee opinion. *Fertil Steril* 2013; **100**: 935-939 [PMID: 24074538 DOI: 10.1016/j.fertnstert.2013.08.038]
90 **Cyranoski D**. Fetal-cell therapy: paper chase. *Nature* 2005; **437**: 810-811 [PMID: 16208340 DOI: 10.1038/437810a]
91 **Huang H**, Chen L, Wang H, Xiu B, Li B, Wang R, Zhang J, Zhang F, Gu Z, Li Y, Song Y, Hao W, Pang S, Sun J. Influence of patients' age on functional recovery after transplantation of olfactory ensheathing cells into injured spinal cord injury. *Chin Med J* (Engl) 2003; **116**: 1488-1491 [PMID: 14570607]
92 **Dobkin BH**, Curt A, Guest J. Cellular transplants in China: observational study from the largest human experiment in chronic spinal cord injury. *Neurorehabil Neural Repair* 2006; **20**: 5-13 [PMID: 16467274 DOI: 10.1177/1545968305284675]
93 **Curt A**, Dietz V. Controversial treatments for spinal-cord injuries. *Lancet* 2005; **365**: 841 [PMID: 15752519 DOI: 10.1016/S0140-6736(05)71031-X]
94 **Chapman AR**, Scala CC. Evaluating the first-in-human clinical trial of a human embryonic stem cell-based therapy. *Kennedy Inst Ethics J* 2012; **22**: 243-261 [PMID: 23285793 DOI: 10.1353/ken.2012.0013]
95 **Zhang X**, Hirai M, Cantero S, Ciubotariu R, Dobrila L, Hirsh A, Igura K, Satoh H, Yokomi I, Nishimura T, Yamaguchi S, Yoshimura K, Rubinstein P, Takahashi TA. Isolation and characterization of mesenchymal stem cells from human umbilical cord blood: reevaluation of critical factors for successful isolation and high ability to proliferate and differentiate to chondrocytes as compared to mesenchymal stem cells from bone marrow and adipose tissue. *J Cell Biochem* 2011; **112**: 1206-1218 [PMID: 21312238 DOI: 10.1002/jcb.23042]
96 **Lee MW**, Yang MS, Park JS, Kim HC, Kim YJ, Choi J. Isolation of mesenchymal stem cells from cryopreserved human umbilical cord blood. *Int J Hematol* 2005; **81**: 126-130 [PMID: 15765780 DOI: 10.1532/IJH97.A10404]
97 **Sekiya I**, Larson BL, Smith JR, Pochampally R, Cui JG,

Prockop DJ. Expansion of human adult stem cells from bone marrow stroma: conditions that maximize the yields of early progenitors and evaluate their quality. *Stem Cells* 2002; **20**: 530-541 [PMID: 12456961 DOI: 10.1634/stemcells.20-6-530]

98 **Carrade DD**, Affolter VK, Outerbridge CA, Watson JL, Galuppo LD, Buerchler S, Kumar V, Walker NJ, Borjesson DL. Intradermal injections of equine allogeneic umbilical cord-derived mesenchymal stem cells are well tolerated and do not elicit immediate or delayed hypersensitivity reactions. *Cytotherapy* 2011; **13**: 1180-1192 [PMID: 21899391 DOI: 10.3109/14653249.2011.602338]

99 **Krampera M**, Glennie S, Dyson J, Scott D, Laylor R, Simpson E, Dazzi F. Bone marrow mesenchymal stem cells inhibit the response of naive and memory antigen-specific T cells to their cognate peptide. *Blood* 2003; **101**: 3722-3729 [PMID: 12506037 DOI: 10.1182/blood-2002-07-2104]

100 **Malgieri A**, Kantzari E, Patrizi MP, Gambardella S. Bone marrow and umbilical cord blood human mesenchymal stem cells: state of the art. *Int J Clin Exp Med* 2010; **3**: 248-269 [PMID: 21072260]

101 **Kang KN**, Lee JY, Kim da Y, Lee BN, Ahn HH, Lee B, Khang G, Park SR, Min BH, Kim JH, Lee HB, Kim MS. Regeneration of completely transected spinal cord using scaffold of poly(D,L-lactide-co-glycolide)/small intestinal submucosa seeded with rat bone marrow stem cells. *Tissue Eng Part A* 2011; **17**: 2143-2152 [PMID: 21529281 DOI: 10.1089/ten.tea.2011.0122]

102 **Urdzíková LM**, Růžička J, LaBagnara M, Kárová K, Kubinová Š, Jiráková K, Murali R, Syková E, Jhanwar-Uniyal M, Jendelová P. Human mesenchymal stem cells modulate inflammatory cytokines after spinal cord injury in rat. *Int J Mol Sci* 2014; **15**: 11275-11293 [PMID: 24968269 DOI: 10.3390/ijms150711275]

103 **Cui B**, Li E, Yang B, Wang B. Human umbilical cord blood-derived mesenchymal stem cell transplantation for the treatment of spinal cord injury. *Exp Ther Med* 2014; **7**: 1233-1236 [PMID: 24940417]

104 **Gao S**, Ding J, Xiao HJ, Li ZQ, Chen Y, Zhou XS, Wang JE, Wu J, Shi WZ. Anti-inflammatory and anti-apoptotic effect of combined treatment with methylprednisolone and amniotic membrane mesenchymal stem cells after spinal cord injury in rats. *Neurochem Res* 2014; **39**: 1544-1552 [PMID: 24890008 DOI: 10.1007/s11064-014-1344-9]

105 **Jia Y**, Wu D, Zhang R, Shuang W, Sun J, Hao H, An Q, Liu Q. Bone marrow-derived mesenchymal stem cells expressing the Shh transgene promotes functional recovery after spinal cord injury in rats. *Neurosci Lett* 2014; **573**: 46-51 [PMID: 24837681 DOI: 10.1016/j.neulet.2014.05.010]

106 **Menezes K**, Nascimento MA, Gonçalves JP, Cruz AS, Lopes DV, Curzio B, Bonamino M, de Menezes JR, Borojevic R, Rossi MI, Coelho-Sampaio T. Human mesenchymal cells from adipose tissue deposit laminin and promote regeneration of injured spinal cord in rats. *PLoS One* 2014; **9**: e96020 [PMID: 24830794 DOI: 10.1371/journal.pone.0096020]

107 **Nakajima H**, Uchida K, Guerrero AR, Watanabe S, Sugita D, Takeura N, Yoshida A, Long G, Wright KT, Johnson WE, Baba H. Transplantation of mesenchymal stem cells promotes an alternative pathway of macrophage activation and functional recovery after spinal cord injury. *J Neurotrauma* 2012; **29**: 1614-1625 [PMID: 22233298 DOI: 10.1089/neu.2011.2109]

108 **Mothe AJ**, Bozkurt G, Catapano J, Zabojova J, Wang X, Keating A, Tator CH. Intrathecal transplantation of stem cells by lumbar puncture for thoracic spinal cord injury in the rat. *Spinal Cord* 2011; **49**: 967-973 [PMID: 21606931 DOI: 10.1038/sc.2011.46]

109 **Boido M**, Garbossa D, Fontanella M, Ducati A, Vercelli A. Mesenchymal stem cell transplantation reduces glial cyst and improves functional outcome after spinal cord compression. *World Neurosurg* 2014; **81**: 183-190 [PMID: 23022648 DOI: 10.1016/j.wneu.2012.08.014]

110 **Gu W**, Zhang F, Xue Q, Ma Z, Lu P, Yu B. Transplantation of bone marrow mesenchymal stem cells reduces lesion volume and induces axonal regrowth of injured spinal cord. *Neuropathology* 2010; **30**: 205-217 [PMID: 19845866 DOI: 10.1111/j.1440-1789.2009.01063.x]

111 **Hu SL**, Luo HS, Li JT, Xia YZ, Li L, Zhang LJ, Meng H, Cui GY, Chen Z, Wu N, Lin JK, Zhu G, Feng H. Functional recovery in acute traumatic spinal cord injury after transplantation of human umbilical cord mesenchymal stem cells. *Crit Care Med* 2010; **38**: 2181-2189 [PMID: 20711072 DOI: 10.1097/CCM.0b013e3181f17c0e]

112 **Reubinoff BE**, Itsykson P, Turetsky T, Pera MF, Reinhartz E, Itzik A, Ben-Hur T. Neural progenitors from human embryonic stem cells. *Nat Biotechnol* 2001; **19**: 1134-1140 [PMID: 11731782 DOI: 10.1038/nbt1201-1134]

113 **Cao QL**, Zhang YP, Howard RM, Walters WM, Tsoulfas P, Whittemore SR. Pluripotent stem cells engrafted into the normal or lesioned adult rat spinal cord are restricted to a glial lineage. *Exp Neurol* 2001; **167**: 48-58 [PMID: 11161592 DOI: 10.1006/exnr.2000.7536]

114 **Nemati SN**, Jabbari R, Hajinasrollah M, Zare Mehrjerdi N, Azizi H, Hemmesi K, Moghiminasr R, Azhdari Z, Talebi A, Mohitmafi S, Vosough Taqi Dizaj A, Sharifi G, Baharvand H, Rezaee O, Kiani S. Transplantation of adult monkey neural stem cells into a contusion spinal cord injury model in rhesus macaque monkeys. *Cell J* 2014; **16**: 117-130 [PMID: 24567941]

115 **Lee Y**, Lee S, Lee SR, Park K, Hong Y, Lee M, Park S, Jin Y, Chang KT, Hong Y. Beneficial effects of melatonin combined with exercise on endogenous neural stem/progenitor cells proliferation after spinal cord injury. *Int J Mol Sci* 2014; **15**: 2207-2222 [PMID: 24487506 DOI: 10.3390/ijms15022207]

116 **Piltti KM**, Salazar DL, Uchida N, Cummings BJ, Anderson AJ. Safety of human neural stem cell transplantation in chronic spinal cord injury. *Stem Cells Transl Med* 2013; **2**: 961-974 [PMID: 24191264 DOI: 10.5966/sctm.2013-0064]

117 **Moviglia GA**, Fernandez Viña R, Brizuela JA, Saslavsky J, Vrsalovic F, Varela G, Bastos F, Farina P, Etchegaray G, Barbieri M, Martinez G, Picasso F, Schmidt Y, Brizuela P, Gaeta CA, Costanzo H, Moviglia Brandolino MT, Merino S, Pes ME, Veloso MJ, Rugilo C, Tamer I, Shuster GS. Combined protocol of cell therapy for chronic spinal cord injury. Report on the electrical and functional recovery of two patients. *Cytotherapy* 2006; **8**: 202-209 [PMID: 16793729 DOI: 10.1080/14653240600736048]

118 **Saito F**, Nakatani T, Iwase M, Maeda Y, Hirakawa A, Murao Y, Suzuki Y, Onodera R, Fukushima M, Ide C. Spinal cord injury treatment with intrathecal autologous bone marrow stromal cell transplantation: the first clinical trial case report. *J Trauma* 2008; **64**: 53-59 [PMID: 18188099 DOI: 10.1097/TA.0b013e31815b847d]

119 **Pal R**, Venkataramana NK, Bansal A, Balaraju S, Jan M, Chandra R, Dixit A, Rauthan A, Murgod U, Totey S. Ex vivo-expanded autologous bone marrow-derived mesenchymal stromal cells in human spinal cord injury/paraplegia: a pilot clinical study. *Cytotherapy* 2009; **11**: 897-911 [PMID: 19903102 DOI: 10.3109/14653240903253857]

120 **Ra JC**, Shin IS, Kim SH, Kang SK, Kang BC, Lee HY, Kim YJ, Jo JY, Yoon EJ, Choi HJ, Kwon E. Safety of intravenous infusion of human adipose tissue-derived mesenchymal stem cells in animals and humans. *Stem Cells Dev* 2011; **20**: 1297-1308 [PMID: 21303266 DOI: 10.1089/scd.2010.0466]

121 **Saito F**, Nakatani T, Iwase M, Maeda Y, Murao Y, Suzuki Y, Fukushima M, Ide C. Administration of cultured autologous bone marrow stromal cells into cerebrospinal fluid in spinal injury patients: a pilot study. *Restor Neurol Neurosci* 2012; **30**: 127-136 [PMID: 22232031 DOI: 10.3233/RNN-2011-0629]

122 **Karamouzian S**, Nematollahi-Mahani SN, Nakhaee N,

Eskandary H. Clinical safety and primary efficacy of bone marrow mesenchymal cell transplantation in subacute spinal cord injured patients. *Clin Neurol Neurosurg* 2012; **114**: 935-939 [PMID: 22464434 DOI: 10.1016/j.clineuro.2012.02.003]

P- Reviewer: Peng BG, Wang Y **S- Editor**: Ji FF **L- Editor**: A
E- Editor: Lu YJ

Published by **Baishideng Publishing Group Inc**
8226 Regency Drive, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
http://www.wjgnet.com

© 2015 Baishideng Publishing Group Inc. All rights reserved.