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Stem cell transplantation for treating spinal cord injury

A literature comparison between studies of stem cells obtained from various sources[★]

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Abstract

OBJECTIVE: To identify global research trends of stem cell transplantation for treating spinal cord injury using a bibliometric analysis of the Web of Science.

DATA RETRIEVAL: We performed a bibliometric analysis of data retrievals for stem cell transplantation for treating spinal cord injury from 2002 to 2011 using the Web of Science.

SELECTION CRITERIA: Inclusion criteria: (a) peer-reviewed articles on stem cell transplantation for treating spinal cord injury that were published and indexed in the Web of Science; (b) type of articles: original research articles, reviews, meeting abstracts, proceedings papers, book chapters, editorial material, and news items; and (c) year of publication: 2002–2011. Exclusion criteria: (a) articles that required manual searching or telephone access; (b) documents that were not published in the public domain; and (c) a number of corrected papers from the total number of articles.

MAIN OUTCOME MEASURES: (1) Annual publication output; (2) distribution according to country; (3) distribution according to institution; (4) distribution according to journals; (5) distribution according to funding agencies; and (6) top cited articles over the last 10 years.

RESULTS: Bone marrow mesenchymal stem cells and embryonic stem cells have been widely used for treating spinal cord injury. In total, 191 studies of bone marrow mesenchymal stem cell transplantation and 236 studies of embryonic stem cell transplantation for treating spinal cord injury appeared in the Web of Science from 2002 to 2011, and almost half of which were derived from American or Japanese authors and institutes. The number of studies of stem cell transplantation for treating spinal cord injury has gradually increased over the past 10 years. Most papers on stem cell transplantation for treating spinal cord injury appeared in journals with a particular focus on stem cell research, such as *Stem Cells* and *Cell Transplantation*. Although umbilical cord blood stem cells and adipose-derived stem cells have been studied for treating spinal cord injury, the number of published papers was much smaller, with only 21 and 17 records, respectively, in the Web of Science.

CONCLUSION: Based on our analysis of the literature and research trends, we found that stem cells transplantation obtained from various sources have been studied for treating spinal cord injury; however, it is difficult for researchers to reach a consensus on this theme.

Key Words

bone marrow mesenchymal stem cells; embryonic stem cells; umbilical cord blood-derived mesenchymal stem cells; adipose-derived mesenchymal stem cells; cell transplantation; spinal cord injury; bibliometric; Web of Science; neural regeneration

Abbreviations

BMMSCs, bone marrow mesenchymal stem cells; ESCs, embryonic stem cells

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INTRODUCTION

Spinal cord injury is a serious trauma to the central nervous system, which presents with high incidence, disability and cost. It is a serious hazard to human health, and places a heavy burden on patients and their families. Spinal cord injury causes the loss of numerous spinal neurons, and there is a lack of neurogenesis to promote spinal repair. Maintaining cell survival, regenerating axons, positioning regenerated axons, and rebuilding synapses are the main difficulties for functional recovery after spinal injury^[1]. Although various methods including surgery, medication and physical rehabilitation are performed for the treatment of spinal injury, there is not an ideal effective method to cure spinal injury. Tissue-engineered cell transplantation provides a new approach for treating spinal cord injury, which may repair or regenerate injured axons and recover partial spinal functions. Currently, bone marrow mesenchymal stem cells (BMMSCs), embryonic stem cells (ESCs), and umbilical cord blood stem cells are used for treating spinal cord injury. BMMSCs have a good differentiation capacity, and transplanted BMMSCs can partially repair neural functions^[2]. Brazelton *et al*^[3] found that exogenous BMMSCs differentiate into glial cells and neurons after transplantation into mouse brain, suggesting that BMMSC transplantation can be used for treating spinal cord injury. Sasaki *et al*^[4] used BMMSC transplantation to treat spinal cord injury and found that BMMSCs can repair the myelin sheath of damaged spinal axons. Neural stem cells show special features due to isogenesis with cells in spinal areas^[5]. Thus, BMMSC transplantation has been the study focus of an increasing number of researchers^[6-7]. Additionally, gene-modified neural stem cells have been applied in clinical studies that mainly focus on providing a suitable microenvironment for stem cells in damaged spinal cord^[8-9]. The mechanisms of cell transplantation, which promote neural regeneration in damaged spinal function include: (1) Providing necessary conditions for neuronal and axonal regeneration; (2) To substitute or generate new neurons to form new synapses; and (3) To guide axons for alignment in order in tissue-engineered scaffolds to form new synapses. In damaged spinal cord, interneurons derived from stem cells provide a bridge to possibly reconnect the damaged spinal cord and recover spinal functions^[10-13]. Zuk *et al*^[14] isolated adipose-derived mesenchymal stem cells and found that they can be induced to differentiate into neuron-like cells. Furthermore, Safford *et al*^[15] found that adipose-derived mesenchymal stem cells can be induced to differentiate into neurons and cells from other tissues.

DATA SOURCES AND METHODOLOGY

Data retrieval

In this study, we used bibliometric analyses to quantitatively and qualitatively investigate research trends in studies of stem cell transplantation for treating spinal cord injury. For this purpose, we employed the Web of Science, a research database of publications and citations that are selected and evaluated by the Institute for Scientific Information in Philadelphia, PA, USA, using the key words “bone marrow mesenchymal stem cells” “embryonic stem cells” “umbilical cord blood derived mesenchymal stem cells” “adipose derived mesenchymal stem cells” “cell transplantation” and “spinal cord injury”. We limited the period of publication from 2002 to 2011 to compile a bibliography of all articles related to stem cell transplantation for treating spinal cord injury. We downloaded the data on March 25, 2012.

Inclusion criteria

The inclusion criteria were as follows: (1) Peer-reviewed articles on stem cell transplantation for treating spinal cord injury, which were published and indexed in the Web of Science, including original research articles, reviews, meeting abstracts, proceedings papers, book chapters, editorial material, and news items; (2) the year of publication was 2002–2011; and (3) the citation database was Science Citation Index-Expanded.

Exclusion criteria

We excluded articles that required manual searching or telephone access, documents that were not published in the public domain, and a number of corrected papers from the total number of articles analyzed.

The outcomes of all articles referring to stem cell transplantation for treating spinal cord injury were measured using the following criteria. (a) Annual publication output on stem cell transplantation for treating spinal cord injury, included in the Web of Science from 2002 to 2011; (b) publications on stem cell transplantation for treating spinal cord injury in the Web of Science from 2002 to 2011 according to country. (c) publications on stem cell transplantation for treating spinal cord injury in the Web of Science from 2002 to 2011, by institution; (d) distribution of publications on stem cell transplantation for treating spinal cord injury in the Web of Science from 2002 to 2011 by funding agencies; and (e) the most cited papers on stem cell transplantation for treating spinal cord injury in the Web of Science from 2002 to 2011.

RESULTS

Search results of publications addressing stem cells obtained from different sources for treating spinal cord injury from 2002 to 2011 (Table 1)

Table 1 Number of publications addressing stem cells obtained from different sources for treating spinal cord injury included in the Web of Science from 2002 to 2011

Query formulation	Number of publication
ts=("bone marrow stem cell*" or "bone marrow mesenchymal stem cell*" or "bone mesenchymal stem cell*" or "bone marrow stromal cell*" or "BMSC" or "BMSCs" or "BMHSCs") and ts=("spinal cord injury" or "spinal injury" or "spinal transection" or "spinal cord transection")	191
ts(("embryonic stem cell*" or "embryonic-like stem cell*" or "embryonic pluripotent stem cell*" or "ESCs" or "ELSC" or "EPSC") same ("spinal cord injury" or "spinal injury" or "spinal transection" or "spinal cord transection"))	236
ts(("umbilical cord blood stem cell*" or "cord blood stem cell*" or "umbilical cord blood derived mesenchymal stem cell*" or "umbilical cord blood hematopoietic stem cell*" or "hematopoietic progenitor cell*" or "CB-SCs" or "UCB-MSCs" or "UCB-MS") same ("spinal cord injury" or "spinal injury" or "spinal transection" or "spinal cord transection"))	21
ts(("adipose derived stem cell*" or "adipose derived mesenchymal stem cell*" or "ADSCs" or "ADMSC" or "ADMSCs" or "adipose tissue-derived stromal cell*") same ("spinal cord injury" or "spinal injury" or "spinal transection" or "spinal cord transection"))	17

Annual publication output of BMMSC transplantation for treating spinal cord injury from 2002 to 2011 (Figure 1)

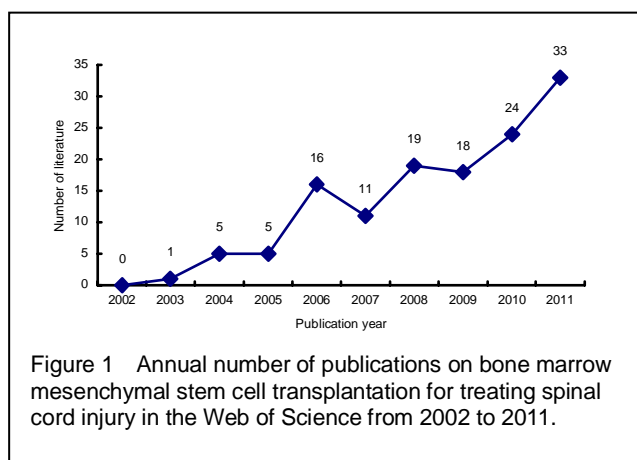


Figure 1 Annual number of publications on bone marrow mesenchymal stem cell transplantation for treating spinal cord injury in the Web of Science from 2002 to 2011.

There were 191 publications on BMMSC transplantation for treating spinal cord injury in the Web of Science from 2002 to 2011. The number of publications on BMMSC transplantation for treating spinal cord injury has gradually increased over the past 10 years. In total, no

papers were published and included in the Web of Science in 2002, but the number of published papers increased to 33 in 2011. However, there was a slight decrease in the number of papers published in 2005 and 2007.

Publication distribution of countries and institutes based on BMMSC transplantation for treating spinal cord injury from 2002 to 2011 (Table 2 and Figure 2)

Table 2 The top 10 countries on bone marrow mesenchymal stem cell transplantation for treating spinal cord injury from 2002 to 2011

Country	Number of publication	% of total publication
Japan	34	25.75
China	33	25.00
USA	27	20.45
South Korea	10	7.57
Spain	7	5.30
Canada	5	3.78
Czech Republic	4	3.03
Iran	4	3.03
Netherlands	4	3.03
Germany	3	2.27

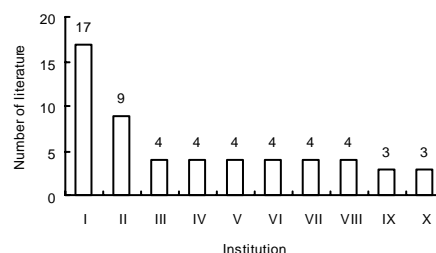


Figure 2 The top 10 institutes for publications on BMMSC transplantation for treating spinal cord injury from 2002 to 2011.

I: Hokkaido University; II: Sun Yat-sen University; III: Autonomous University of Madrid; IV: Chiba University; V: China Medical University; VI: Hiroshima University; VII: Kyoto University; VIII: Radboud University Nijmegen; IX: Aino University; X: Chonbuk National University.

The contribution analysis of different countries/territories for publications was based on journal articles in which the address and affiliation of at least one author were provided. The total number of articles analyzed by country and institute publications was 191.

From Table 2, it is clear that Japan published the most papers on BMMSC transplantation for treating spinal cord injury. Japan published 34 papers that accounted for 25.75% of the total, which was much higher than the number of publications by other countries. China ranked second with 33 papers that accounted for 25%. The USA published 27 papers and ranked third. Hokkaido University, Sun Yat-sen University and the

Autonomous University of Madrid were the most prolific research institutes for publications on BMMSC transplantation for treating spinal cord injury. Among the top 10 research institutes publishing in this field, four are in Japan, two are in China, two are in South Korea, and there is one institute each in Spain and the Netherlands.

Most cited articles on BMMSC transplantation for treating spinal cord injury from 2002 to 2011 (Table 3)

Table 3 Articles with more than 60 total citations on bone marrow mesenchymal stem cell transplantation for treating spinal cord injury in the Web of Science from 2002 to 2011

Title	Journal	Publication year	Total citation
Bone marrow stromal cells infused into the cerebrospinal fluid promote functional recovery of the injured rat spinal cord with reduced cavity formation ^[16]	<i>Experimental Neurology</i>	2004	117
Migration and differentiation of nuclear fluorescence-labeled bone marrow stromal cells after transplantation into cerebral infarct and spinal cord injury in mice ^[17]	<i>Neuropathology</i>	2003	90
Recovery of function following grafting of human bone marrow-derived stromal cells into the injured spinal cord ^[18]	<i>Neurorehabilitation and Neural Repair</i>	2006	81
Transplantation of bone marrow stem cells as well as mobilization by granulocyte-colony stimulating factor promotes recovery after spinal cord injury in rats ^[19]	<i>Journal of Neurotrauma</i>	2006	79
Transplantation of bone marrow stromal cell-derived Schwann cells promotes axonal regeneration and functional recovery after complete transection of adult rat spinal cord ^[20]	<i>Journal of Neuropathology and Experimental Neurology</i>	2005	67
Functional recovery in chronic paraplegia after bone marrow stromal cells transplantation ^[21]	<i>Neuroreport</i>	2004	63
Bone marrow stem cells and polymer hydrogels-two strategies for spinal cord injury repair ^[22]	<i>Cellular and Molecular Neurobiology</i>	2006	60

Among the seven articles with more than 60 citations, the article “bone marrow stromal cells infused into the cerebrospinal fluid promote functional recovery of the injured rat spinal cord with reduced cavity formation”, published in 2004, was cited 117 times, which was more times than any other article.

Most funding support for BMMSC transplantation for treating spinal cord injury from 2002 to 2011 (Table 4)

Table 4 Funding agencies on bone marrow mesenchymal stem cell transplantation for treating spinal cord injury from 2002 to 2011

Funding agency	Number of publication	% of total publication
Ministry of Education Science and Culture of Japan	12	9.09
National Natural Science Foundation of China	8	6.06
Chinese National Natural Science Foundation	3	2.27
Christopher Reeve Paralysis Foundation	2	1.51
Japanese Ministry of Education Culture Sports Science and Technology	2	1.51
Ministry of Education Science and Technology	2	1.51
Netherlands Organization for Scientific Research	2	1.51
NIH	2	1.51
Administration of Traditional Chinese Medicine of Guangdong Province of China	1	0.75

Among the publications, 12 articles were supported by the Ministry of Education, Culture, Sports, Science and Technology of Japan, and eight articles were supported by the National Natural Science Foundation of China.

Journals that published on BMMSC transplantation for treating spinal cord injury from 2002 to 2011 (Table 5)

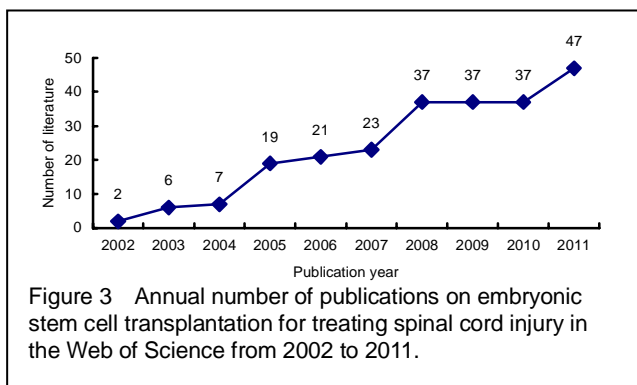
Table 5 Top 14 journals that published studies of bone marrow mesenchymal stem cell transplantation for treating spinal cord injury from 2002 to 2011

Journal	Number of paper	% of total publication
<i>Cell Transplantation</i>	11	5.76
<i>Journal of Neurotrauma</i>	10	5.24
<i>Experimental Neurology</i>	9	4.71
<i>Neural Regeneration Research</i>	9	4.71
<i>Neuroscience Letters</i>	8	4.19
<i>Neuropathology</i>	7	3.67
<i>Brain Research</i>	6	3.14
<i>Neuroreport</i>	6	3.14
<i>Cytotherapy</i>	5	2.62
<i>Journal of Neuroscience Research</i>	5	2.62
<i>Journal of Neurosurgery Spine</i>	4	2.09
<i>Spine</i>	4	2.09
<i>Stem Cells</i>	4	2.09
<i>Tissue Engineering and Regenerative Medicine</i>	4	2.09

In Table 5, it is evident that most papers on BMMSC transplantation for treating spinal cord injury appeared in journals with a particular focus on neuroscience research.

Cell Transplantation published 11 papers that accounted for 5.76% of the total number of publications, which was followed by the *Journal of Neurotrauma* that published 10 papers and accounted for 5.24%.

Annual publication output for ESC transplantation for treating spinal cord injury from 2002 to 2011 (Figure 3)



There were 236 publications on ESC transplantation for treating spinal cord injury in the Web of Science from 2002 to 2011. The number of publications on ESC transplantation for treating spinal cord injury has gradually increased over the past 10 years. In total, 47 papers were published and included in the Web of Science in 2011, which had increased by more than 20 times than that in 2002.

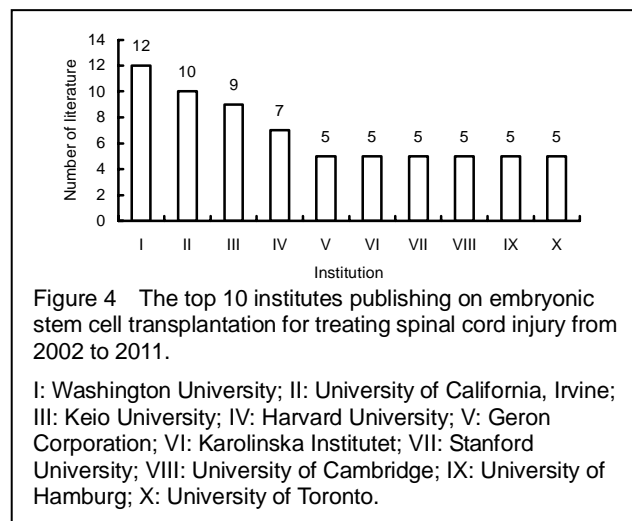
Publication distribution of countries and institutes based on ESC transplantation for treating spinal cord injury from 2002 to 2011 (Table 6 and Figure 4)

Table 6 The top 10 countries on embryonic stem cell transplantation for treating spinal cord injury from 2002 to 2011

Country	Number of publication	% of total publication
USA	110	46.61
Japan	21	8.89
Germany	19	8.05
England	17	7.20
Canada	12	5.08
Italy	10	4.23
China	10	4.23
Australia	9	3.81
Spain	9	3.81
Sweden	9	3.81

The contribution analysis of different countries/territories for publications was based on journal articles in which the address and affiliation of at least one author were provided. The total number of articles analyzed for country and institute publications was 191. The top 10 countries/territories and institutions were then ranked.

In Table 6, it is clear that the USA published the most papers on ESC transplantation for treating spinal cord injury, with 110 papers that accounted for 46.61% of the total, which was much higher than the number of papers published by other countries. Japan ranked second with 21 papers that accounted for 8.89%. Germany published 19 papers and ranked third.



Washington University, University of California, Irvine, and Keio University are the most prolific research institutes publishing on ESC transplantation for treating spinal cord injury. Among the top 10 research institutes publishing in this field, five are in the USA, and the other five are in Japan, Sweden, the UK, Germany and Canada.

Most funding support for ESC transplantation for treating spinal cord injury from 2002 to 2011 (Table 7)

Table 7 Funding support on embryonic stem cell transplantation for treating spinal cord injury in the Web of Science from 2002 to 2011

Funding agency	Number of publication	% of total publication
NIH	13	5.50
CONACYT	3	2.27
National Institutes of Health	3	2.27
Academy of Finland	2	1.51
Aospine North America	2	1.51
California Institute for Regenerative Medicine	2	1.51
Canadian Institutes of Health Research	2	1.51
California Institute for Regenerative Medicine	2	1.51
European Commission	2	1.51

Among the publications, 13 articles were supported by the NIH, and three articles were supported by CONACYT and the National Institutes of Health. The other funding agencies supported less than 2 publications.

Most cited articles on ESC transplantation for treating spinal cord injury from 2002 to 2011 (Table 8)

Table 8 Articles with more than 70 total citations on embryonic stem cell transplantation for treating spinal cord injury in the Web of Science from 2002 to 2011

Title	Journal	Publication year	Total citation
Human embryonic stem cell-derived oligodendrocyte progenitor cell transplants remyelinate and restore locomotion after spinal cord injury ^[23]	<i>Journal of Neuroscience</i>	2005	394
Differentiation of embryonic stem cells to clinically relevant populations: Lessons from embryonic development ^[24]	<i>Cell</i>	2008	372
Therapeutic interventions after spinal cord injury ^[25]	<i>Nature Reviews Neuroscience</i>	2006	176
Therapeutic potential of embryonic stem cells ^[26]	<i>Blood Reviews</i>	2005	86
Experimental strategies to promote spinal cord regeneration - an integrative perspective ^[27]	<i>Progress in Neurobiology</i>	2006	84
Updates on stem cells and their applications in regenerative medicine ^[28]	<i>Journal of Tissue Engineering and Regenerative Medicine</i>	2008	78
Stem cell-based cell therapy in neurological diseases: a review ^[29]	<i>Journal of Neuroscience Research</i>	2009	74
Magnetic resonance tracking of implanted adult and embryonic stem cells in injured brain and spinal cord ^[30]	<i>Stem Cell Biology: Development and Plasticity</i>	2005	73
The differentiation of embryonic stem cells seeded on electrospun nanofibers into neural lineages ^[31]	<i>Biomaterials</i>	2009	70

Among the 10 articles with more than 70 citations, the article "Human embryonic stem cell-derived oligodendrocyte progenitor cell transplants remyelinate and restore locomotion after spinal cord injury", published in 2005, was cited 394 times, which was greater than any other article.

Journals that published on ESC transplantation for treating spinal cord injury from 2002 to 2011

(Table 9)

In Table 9, it is evident that most papers on ESC transplantation for treating spinal cord injury appeared in journals such as *Stem Cells*, *Cell Transplantation* and *PLoS One*.

Highly cited papers on other sources of stem cells for transplantation to treat spinal cord injury (Tables 10 and 11)

Table 9 Top 17 journals that published studies of embryonic stem cell transplantation for treating spinal cord injury from 2002 to 2011

Journal	Number of paper	% of total publication
<i>Stem Cells</i>	15	6.36
<i>Cell Transplantation</i>	12	5.09
<i>PLoS One</i>	11	4.66
<i>Journal of Neurotrauma</i>	9	3.81
<i>Experimental Neurology</i>	5	2.12
<i>Journal of Neuroscience Research</i>	5	2.12
<i>Cytotherapy</i>	3	1.27
<i>European Journal of Neuroscience</i>	3	1.27
<i>Frontiers in Bioscience Landmark</i>	3	1.27
<i>Neurological Research</i>	3	1.27
<i>Neuroscience</i>	3	1.27
<i>Neurotherapeutics</i>	3	1.27
<i>Philosophical Transactions of the Royal Society B Biological Sciences</i>	3	1.27
<i>Progress in Brain Research</i>	3	1.27
<i>Progress in Neurobiology</i>	3	1.27
<i>Regenerative Medicine</i>	3	1.27
<i>Stem Cell Reviews</i>	3	1.27

Table 10 Top eight articles on umbilical cord blood stem cell transplantation for treating spinal cord injury in the Web of Science from 2002 to 2011

Title	Journal	Publication year	Total citation
Human umbilical cord blood stem cells infusion in spinal cord injury: Engraftment and beneficial influence on behavior ^[32]	<i>Journal of Hematology & Stem Cell Research</i>	2003	110
Plasticity and therapeutic potential of mesenchymal stem cells in the nervous system ^[33]	<i>Current Pharmaceutical Design</i>	2005	81
Axonal remyelination by cord blood stem cells after spinal cord injury ^[34]	<i>Journal of Neurotrauma</i>	2007	36
Cellular MRI and its role in stem cell therapy ^[35]	<i>Regenerative Medicine</i>	2008	31
Umbilical cord blood stem cell mediated downregulation of Fas improves functional recovery of rats after spinal cord injury ^[36]	<i>Neurochemical Research</i>	2008	26
Transplantation of canine umbilical cord blood-derived mesenchymal stem cells in experimentally induced spinal cord injured dogs ^[37]	<i>Journal of Veterinary Science</i>	2007	23
Cord blood stem cells: A review of potential neurological applications ^[38]	<i>Stem Cell Reviews</i>	2008	23
The potential of cord blood stem cells for use in regenerative medicine ^[39]	<i>Expert Opinion on Biological Therapy</i>	2007	22

Table 11 Top four articles on adipose derived stem cell transplantation for treating spinal cord injury in the Web of Science from 2002 to 2011

Title	Journal	Publication year	Total citation
Autologous adipose tissue-derived stromal cells for treatment of spinal cord injury ^[40]	<i>Stem Cells and Development</i>	2006	46
Neuronal differentiation potential of human adipose-derived mesenchymal stem cells ^[41]	<i>Stem Cells and Development</i>	2008	38
The differentiation of rat adipose-derived stem cells into OEC-like cells on collagen scaffolds by co-culturing with OECs ^[42]	<i>Neuroscience Letters</i>	2007	20
Functional neural differentiation of human adipose tissue-derived stem cells using bFGF and forskolin ^[43]	<i>BMC Cell Biology</i>	2010	16

DISCUSSION

Based on our bibliometric analysis of the Web of Science, we found the following research trends for studies of stem cell transplantation for treating spinal cord injury over the past 10 years.

BMMSCs and ESCs are widely used for treating spinal cord injury, with 191 studies of BMMSC transplantation and 236 studies of ESC transplantation for treating spinal cord injury appearing in the Web of Science from 2002 to 2011, and almost half of which are from American or Japanese authors and institutes. Although umbilical cord blood stem cells and adipose-derived stem cells have been studied for treating spinal cord injury, the published papers are much fewer, with only 21 and 17 records, respectively, which are included in the Web of Science.

The number of studies of stem cell transplantation for treating spinal cord injury has gradually increased over the past 10 years. Most papers on stem cell transplantation for treating spinal cord injury are in journals with a particular focus on stem cell research, such as *Stem Cells* and *Cell Transplantation*. Much attention and effort has been devoted to spinal cord injury treatment using stem cell transplantation. The findings of the present study may be of interest to fellow researchers who are currently undertaking studies of stem cell transplantation for treating spinal cord injury or those who may do so in the future.

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Author contributions: Liangbi Xiang retrieved the references,

extracted the data, conceived and designed the study, and wrote the manuscript. Yu Chen contributed to the review, conception and design, paper revision, and study instruction.

Conflicts of interest: None declared.

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