NEURAL REGENERATION RESEARCH
Volume 7, Issue 16, June 2012
www.nrronline.org

Cite this article as: Neural Regen Res. 2012;7(16):1264-1271.

Application of magnetic resonance imaging for monitoring stem cell transplantation for the treatment of cerebral ischemia★

Xianglin Zhang, Gang Wang, Furen Dong, Zhiming Wang

1Department of Radiology, First Affiliated Hospital of Liaoning Medical University, Jinzhou 121001, Liaoning Province, China
2Third Affiliated Hospital of Liaoning Medical University, Jinzhou 121001, Liaoning Province, China

Abstract

OBJECTIVE: To identify global research trends in the application of MRI for monitoring stem cell transplantation using a bibliometric analysis of Web of Science.
DATA RETRIEVAL: We performed a bibliometric analysis of studies relating to the application of MRI for detecting stem cell transplantation for the treatment of cerebral ischemia using papers in Web of Science published from 2002 to 2011.
SELECTION CRITERIA: The inclusion criteria were: (a) peer-reviewed articles on the application of MRI for detecting transplanted stem cells published and indexed in Web of Science; (b) year of publication between 2002 and 2011. Exclusion criteria were: (a) articles that required manual searching or telephone access; (b) some corrected papers.
MAIN OUTCOME MEASURES: (1) Annual publication output; (2) distribution according to journals; (3) distribution according to institution; (4) distribution according to country; (5) top cited authors over the last 10 years.
RESULTS: A total of 1 498 studies related to the application of MRI for monitoring stem cell transplantation appeared in Web of Science from 2002 to 2011, almost half of which were derived from American authors and institutes. The number of studies on the application of MRI for detecting stem cell transplantation has gradually increased over the past 10 years. Most papers on this topic appeared in *Magnetic Resonance in Medicine*.
CONCLUSION: This analysis suggests that few experimental studies have been investigated the use of MRI for tracking SPIO-labeled human umbilical cord blood-derived mesenchymal stem cells during the treatment of cerebral ischemia.

Key Words

neural stem cells; embryonic stem cells; bone marrow mesenchymal stem cells; cell transplantation; cerebral ischemia; Web of Science; neural regeneration

Abbreviations

MSCs, mesenchymal stem cells; UCB-MSCs, umbilical cord blood-derived MSCs; SPIO, superparamagnetic iron oxide

Xianglin Zhang★, Master, Professor, Chief physician, Master's supervisor, Department of Radiology, First Affiliated Hospital of Liaoning Medical University, Jinzhou 121001, Liaoning Province, China

Corresponding author: Zhiming Wang, Master, Professor, Chief physician, Master's supervisor, Third Affiliated Hospital of Liaoning Medical University, Jinzhou 121001, Liaoning Province, China
zhangxianglinjr1030@126.com

Received: 2012-01-26
Accepted: 2012-04-23
(N20120608004/ZLJ)

Zhang XL, Wang G, Dong FR, Wang ZM. Application of magnetic resonance imaging for monitoring stem cell transplantation for the treatment of cerebral ischemia. Neural Regen Res. 2012;7(16):1264-1271.

www.crter.cn
www.nrronline.org

doi:10.3969/j.issn.1673-5374.2012.16.009

INTRODUCTION

Cerebral ischemia is a common acute cerebrovascular disease. The key to its treatment involves the rescue of dying neurons in the ischemic penumbra and the promotion of injury recovery. Cerebral ischemia is associated with high levels of mortality and disability, and neural cell replacement therapy is the only effective treatment. Neural cell transplantation can rebuild nerve conduction loops and restore some neurological function, possibly *via* the differentiation of transplanted stem cells into functional glial cells or neurons, which can

thus substitute for some of the affected neurons. This replacement therapy also activates endogenous neural stem cells. The transplanted stem cells secrete cytokines to improve the local microenvironment of ischemic necrosis in terms of inflammation, tissue necrosis and glial scarring[1-2]. However, cerebral ischemic damage can affect large areas and many kinds of nerve cells. Ischemic lesions may involve a number of sites in the hypothalamus, striatum, hippocampus and cortex, and reconstruction of this complex system presents a challenge for cell transplantation.

The sources of stem cells to treat cerebral ischemia include embryonic stem cells, bone marrow mesenchymal stem cells (MSCs), human umbilical cord blood (UCB) cells, human adipose mesenchymal cells, and fetal brain central nervous system cells. MSCs differ from hematopoietic stromal cells in that they are pluripotent precursor cells. UCB-derived MSCs (UCB-MSCs) have some advantages, such as strong amplification, convenience and availability, and lack of immune rejection, and they have proven a feasible and effective means of neural cell replacement therapy for cerebral ischemia[3].

Transplanted stem cells show different migration and differentiation patterns under different pathological and physiological conditions in the central nervous system. These characteristics of stem cells have been investigated by sacrificing experimental animals at certain time points after transplantation. However, this invasive method does not allow the dynamic observation of the stem cells in an individual animal. Non-invasive methods are therefore required to monitor transplanted stem cells *in vivo*.

In 1999, Weissleder[4] first proposed the concept of molecular imaging, *i.e*., using modern imaging techniques to carry out real-time microscopic imaging of physiological or pathological processes *in vivo* at a molecular level. MRI demonstrates high resolution at the molecular level and has powerful functional imaging capabilities. MRI is currently widely used for the dynamic monitoring of stem-cell migration, homing, proliferation and differentiation, and to analyze the efficacy and prognosis of stem cell transplantation in damaged zones. There is thus growing emphasis on the prospects of MRI for live-cell tracking[5-6]. The contrast agent superparamagnetic iron oxide (SPIO) nanomaterial forms a core-shell structure with a dextran biopolymer coating. SPIO mainly produces a strong T_2-negative contrast effect. It is characterized by small particle size and strong penetrating power, with a relaxation rate of approximately 7−10 times that of gadolinium under the same conditions. SPIO can produce signal contrast in MRI at very low concentrations. It is also biodegradable with no toxic accumulation; after metabolism, it enters the normal plasma iron pool and combines with red blood cell hemoglobin, or is used in other metabolic processes[7]. Some forms (such as cross-linked iron oxide particles) can also be combined with fluorescent markers to double-label stem cells, or with membrane proteins for imaging of apoptosis[8]. Studies have shown that staining of SPIO magnetically-labeled cells with Prussian blue allowed the SPIO in the cells to be displayed, and the cytoplasm was shown to contain a large number of iron-containing vesicles or endosomes. Investigation of the biological activity of the labeled stem cells confirmed that the labeling had no short- or long-term toxic effects. The viability, differentiation and apoptosis rates of the labeled stem cells were unaffected compared to the unlabeled cells, and did not change over time[9]. A combination of green fluorescent protein and SPIO could effectively mark neural stem cells cultured *in vitro*, and the proliferation and differentiation abilities of double-labeled neural stem cells were similar to those of unlabeled cells[10]. Stoll *et al* [11] used MRI to track the migration of transplanted neural stem cells labeled with ultra-magnetic iron oxide in the host brain *in vivo*. Chen *et al* [12] tracked rat bone marrow-derived neural stem cells labeled with ultra-small SPIO Sinerem and transfection reagent poly-lysine complexes using MRI *in vivo*. Nevertheless, few experimental studies have investigated the use of MRI for tracking SPIO-labeled human UCB-MSCs during the treatment of cerebral ischemia[13].

DATA SOURCES AND METHODOLOGY

Data retrieval

Bibliometric methods were used to quantitatively and qualitatively investigate research trends in the application of MRI for monitoring stem cell transplantation for the treatment of cerebral ischemia. SCI-E is a searchable database of publications maintained by the Institute for Scientific Information in Philadelphia, PA, USA, and was used for this study. SCI-E was searched using the keywords “neural stem cells” “embryonic stem cells” “bone marrow mesenchymal stem cells” “cell transplantation” and “cerebral ischemia”. A bibliography of all articles related to the application of MRI for monitoring stem cell transplantation was compiled for the publication period 2002 to 2011.

Inclusion criteria

Articles closely related to the application of MRI for monitoring stem cell transplantation for the treatment of cerebral ischemia and published between 2002 and 2011 were included.

Exclusion criteria

Articles included in Social Sciences Citation Index, Arts & Humanities Citation Index, Conference Proceedings Citation Index – Science, Conference Proceedings Citation Index – Social Science & Humanities, Current Chemical Reactions, as well as Index Chemicus were excluded.

Web of Science data were performed statistical analysis using Excel. All articles referring to the application of MRI for monitoring stem cells for the treatment of cerebral ischemia that met the inclusion criteria were analyzed regarding output distribution in subject categories and journals, publication outputs of countries and institutes, and citations.

RESULTS

Search results for publications relating to the application of MRI for monitoring stem cell transplantation from 2002 to 2011 (Table 1)

Table 1 Search results for application of MRI for detecting transplanted stem cells in the Web of Science from 2002 to 2011

Query formulation	Number of publication
ts=("MRI" or "magnetic resonance imaging") and ts=("cell transplantation" or "stem cell*")	1 498
ts=("Superparamagnetic iron oxide" or "SPIO") and ts=("cell transplantation" or "stem cell*")	382
ts=("MRI" or magnetic resonance imaging) and ts=(cerebral ischemia or brain ischemia) and Ts=(stem cells or cell transplantation)	79
ts=(Superparamagnetic iron oxide or "SPIO") and ts=("cell transplantation" or "stem cell*") and ts=(cerebral ischemia or brain ischemia)	13
ts=(MRI or magnetic resonance imaging) and ts=(cerebral ischemia or brain ischemia) and ts=("umbilical cord blood stem cell" or "umbilical cord blood stem cells" or "cord blood stem cell" or "cord blood stem cells" or "umbilical cord blood derived mesenchymal stem cell" or "umbilical cord blood derived mesenchymal stem cells" or "umbilical cord blood hematopoietic stem cell" or "umbilical cord blood hematopoietic stem cells" or "hematopoietic progenitor cell" or "hematopoietic progenitor cells" or "CB-SCs" or "UCB-MSCs" or "UCB-MSC")	1

Annual publication output relating to the application of MRI for detecting transplanted stem cells from 2002 to 2011 (Figure 1)

A total of 1 498 publications relating to the application of MRI for detecting transplanted stem cells were identified in Web of Science from 2002 to 2011. The number of publications gradually increased over the past 10 years; only 27 papers were published and included in Web of Science in 2002, which was much fewer than in 2011.

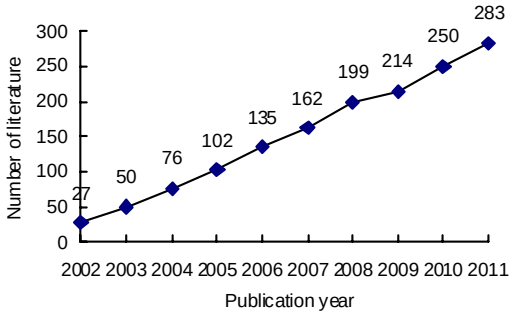

Figure 1 Annual number of publications relating to the application of MRI for detecting transplanted stem cells in Web of Science from 2002 to 2011.

Distribution of published papers relating to the application of MRI for detecting transplanted stem cells according to journal (Table 2)

Table 2 Top 15 journals that published studies related to the application of MRI for detecting transplanted stem cells included in Web of Science from 2002 to 2011

Journal	ISSN	Impact factor	Number of paper	% of total publication
Magnetic Resonance in Medicine	0740-3149	3.268	56	3.74
Circulation	0009-7322	14.432	43	2.87
Biomaterials	0142-9612	7.883	29	1.94
Cell Transplantation	0963-6897	6.204	23	1.54
Neuroimage	1053-8119	5.937	23	1.54
Contrast Media Molecular Imaging	1555-4309	4.020	21	1.40
NMR in Biomedicine	0952-3480	3.064	21	1.40
Molecular Imaging and Biology	1536-1632	3.139	20	1.34
Journal of Magnetic Resonance Imaging	1035-1807	2.794	18	1.20
Journal of the American College of Cardiology	0735-1097	14.293	18	1.20
PLoS One	1932-6203	4.411	17	1.14
Stem Cells	1066-5099	7.871	16	1.07
Blood	0006-4971	10.558	15	1.00
Bone Marrow Transplantation	0268-3369	3.660	15	1.00
European Heart Journal	0195-668X	10.052	15	1.00

From Table 2, it is evident that most papers relating to the application of MRI for detecting transplanted stem cells appeared in *Magnetic Resonance in Medicine*, which published 56 papers, accounting for 3.74% of the total number of publications; this was followed by *Circulation*, which published 43 papers (2.87%).

Distribution of numbers of publications relating to the application of MRI for detecting transplanted stem cells according to country (Table 3)

Table 3 Top 10 countries in terms of numbers of publications relating to the application of MRI for detecting transplanted stem cells in Web of Science from 2002 to 2011

Country	Number of paper	% of total publication
USA	629	41.99
Germany	199	13.28
China	154	10.28
Italy	90	6.01
UK	75	5.01
France	72	4.81
Japan	72	4.81
South Korea	68	4.54
Canada	66	4.41
Netherlands	64	4.27

As seen in Table 3, most papers relating to the application of MRI for detecting transplanted stem cells were published in the USA, with 629 papers, accounting for 41.99% of the total. This output was much higher than the numbers of publications from other countries; Germany ranked second with 199 papers (13.28%) and China ranked third with 154 papers (10.28%).

Numbers of publications relating to the application of MRI for detecting transplanted stem cells according to institution (Table 4)

In Table 4 shows that the top institution for publishing studies on the application of MRI for detecting transplanted stem cells during the period analyzed was Johns Hopkins University, followed by Stanford University.

Distribution of publications relating to the application of MRI for detecting transplanted stem cells according to document type

Table 4 Top 12 institutions in terms of numbers of publications relating to the application of MRI for detecting transplanted stem cells in Web of Science from 2002 to 2011

Institution	Number of paper	% of total publication
Johns Hopkins University	86	5.74
Stanford University	42	2.80
National Institutes of Health	40	2.67
Harvard University	36	2.40
University of Minnesota	31	2.07
University of California, San Francisco	28	1.87
National Heart, Lung, and Blood Institute	26	1.74
University of Pennsylvania	25	1.67
Leiden University	23	1.54
Technical University of Munich	21	1.40
University of Washington	20	1.34
National Institute of Neurological Disorders and Stroke	19	1.27

Seven document types were found among the 1 498 publications from 2002 to 2011. Articles (1 182) were the most frequently used document type comprising 78.91%, followed by reviews (195; 13.02%), meeting abstracts (99; 6.61%), and proceedings papers (63; 4.21%). The remaining types of articles were editorial material (17), letters (5), and book chapters (1).

Most-cited articles relating to the application of MRI for detecting transplanted stem cells (Table 5)

Table 5 Most-cited articles relating to the application of MRI for detecting transplanted stem cells in the Web of Sciencefrom 2002 to 2011

Title	Journal	Publication year	Total citation
Intracoronary autologous bone-marrow cell transfer after myocardial infarction: the BOOST randomised controlled clinical trial[14]	*Lancet*	2004	1 051
Embryonic stem cells develop into functional dopaminergic neurons after transplantation in a Parkinson rat model[15]	*Proceedings of the National Academy of Sciences of the United States of America*	2002	609
Intracoronary injection of mononuclear bone marrow cells in acute myocardial infarction[16]	*New England Journal of Medicine*	2006	570
Transplantation of progenitor cells and regeneration enhancement in acute myocardial infarction-Final one-year results of the TOPCARE-AMI trial[17]	*Journal of the American College of Cardiology*	2004	509
Recent advances in iron oxide nanocrystal technology for medical imaging[18]	*Advanced Drug Delivery Reviews*	2006	410
Monitoring of implanted stem cell migration *in vivo*: A highly resolved *in vivo* magnetic resonance imaging investigation of experimental stroke in rat[19]	*Proceedings of the National Academy of Sciences of the United States of America*	2002	389
In vivo magnetic resonance imaging of mesenchymal stem cells in myocardial infarction[20]	*Circulation*	2003	365
Magnetic resonance tracking of dendritic cells in melanoma patients for monitoring of cellular therapy[21]	*Nature Biotechnology*	2005	317

Annual publication output relating to the application of MRI for detecting transplanted SPIO-labeled stem cells from 2002 to 2011 (Figure 2)

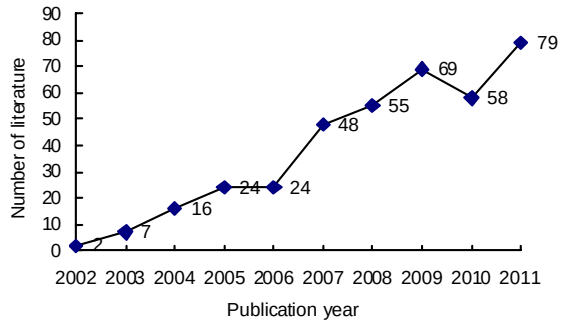

Figure 2 Annual number of publications relating to the application of MRI for detecting transplanted superparamagnetic iron oxide-labeled stem cells in Web of Science from 2002 to 2011.

A total of 382 publications relating to the application of MRI for the detection of transplanted SPIO-labeled stem cells were identified in Web of Science from 2002 to 2011. The numbers of publications gradually increased over the past 10 years, apart from a slight decrease in 2010.

Distribution of published studies relating to the application of MRI for detecting transplanted SPIO-labeled stem cells according to journal (Table 6)

Table 6 Top 10 journals that published studies relating to the application of MRI for detecting transplanted superparamagnetic iron oxide-labeled stem cells in Web of Science from 2002 to 2011

Journal	ISSN	Impact factor	Number of paper	% of total publication
Magnetic Resonance in Medicine	0195-668X	10.052	31	8.12
Molecular Imaging and Biology	1536-1632	3.139	13	3.40
NMR in Biomedicine	0952-3480	3.064	13	3.40
Radiology	0033-8419	6.069	13	3.40
Biomaterials	0142-9612	9.076	12	3.14
Contrast Media Molecular Imaging	1555-4309	4.020	12	3.14
Cell Transplantation	0963-6897	6.204	9	2.36
Journal of Magnetic Resonance Imaging	1053-1807	2.749	9	2.36
Cytotherapy	1465-3249	2.925	8	2.09
Molecular Imaging	1535-3508	3.169	8	2.09

From Table 6 shows that most papers relating to the application of MRI for detecting transplanted SPIO-labeled stem cells appeared in *Magnetic Resonance in Medicine*, which published 31 papers, accounting for 8.12% of the total number of publications; this was followed by *Molecular Imaging and Biology* and *NMR in Biomedicine and Radiology*, which published 13 papers (3.40%) each.

Distribution of publications relating to the application of MRI for detecting transplanted SPIO-labeled stem cells according to country (Figure 3)

As seen in Figure 3, the USA published the highest number of papers (173; 45.29%), followed by China (67; 17.54%) and Germany (62; 16.23%).

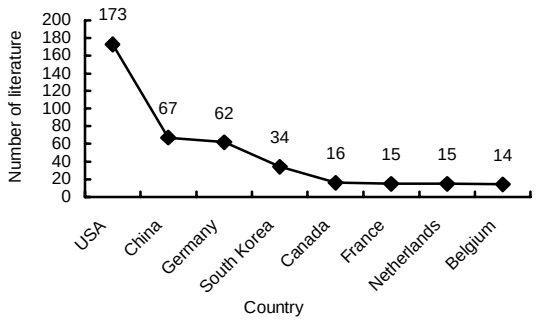

Figure 3 Top eight countries in terms of numbers of studies relating to the application of MRI for detecting transplanted superparamagnetic iron oxide-labeled stem cells included in Web of Science from 2002 to 2011.

Distribution of published studies relating to the application of MRI for detecting transplanted SPIO-labeled stem cells according to institution (Table 7)

Table 7 Top 14 institutions publishing studies relating to the application of MRI for detecting transplanted superparamagnetic iron oxide-labeled stem cells in Web of Science from 2002 to 2011

Institution	Number of paper	% of total publication
Johns Hopkins University	45	11.78
National Institutes of Health	26	6.81
Stanford University	20	5.24
University of Pennsylvania	11	2.88
Southeast University	9	2.36
Harvard University	8	2.09
Henry Ford Health System	8	2.09
INSERM	8	2.09
Philips Research North America	8	2.09
Seoul National University	8	2.09
Technical University of Munich	8	2.09
University Hospital of Tübingen	8	2.09
University of Washington	8	2.09
Yonsei University	8	2.09

As seen in Table 7, Johns Hopkins University was the most productive institution in terms of studies related to the application of MRI for detecting transplanted SPIO-labeled stem cells.

Most-cited articles relating to the application of MRI for detecting transplanted SPIO-labeled stem cells (Table 8)

Table 8 Most-cited articles relating to the application of MRI for detecting transplanted superparamagnetic iron oxide-labeled stem cells in Web of Science from 2002 to 2011

Title	Journal	Publication year	Total citation
Iron oxide MR contrast agents for molecular and cellular imaging[22]	*NMR in Biomedicine*	2004	524
Clinically applicable labeling of mammalian and stem cells by combining; Superparamagnetic iron oxides and transfection agents[23]	*Radiology*	2003	363
Characterization of biophysical and metabolic properties of cells labeled with superparamagnetic iron oxide nanoparticles and transfection agent for cellular MR imaging[24]	*Radiology*	2003	250
Bifunctional magnetic silica nanoparticles for highly efficient human stem cell labeling[25]	*Nano Letters*	2007	203
In vivo magnetic resonance tracking of magnetically labeled cells after transplantation[26]	*Journal of Cerebral Blood Flow and Metabolism*	2002	169
Feridex labeling of mesenchymal stem cells inhibits chondrogenesis but not adipogenesis or osteogenesis[27]	*NMR in Biomedicine*	2004	164

Annual publication output relating to the application of MRI for detecting transplanted stem cells in the treatment of cerebral ischemia from 2002 to 2011 (Figure 4)

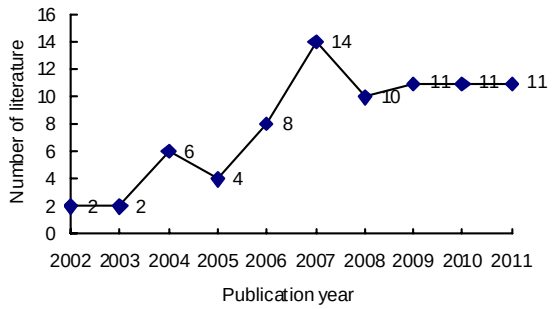

Figure 4 Annual numbers of publications related to the application of MRI for detecting transplanted stem cells in the treatment of cerebral ischemia in Web of Science from 2002 to 2011.

A total of 79 publications relating to the application of MRI for detecting transplanted stem cells in the treatment of cerebral ischemia were identified in Web of Science from 2002 to 2011. The numbers of publications showed an increasing tendency from 2002 to 2007, reached a peak in 2007, (apart from a slight decrease in 2005), then remained steady after 2007.

Distribution of published papers relating to the application of MRI for detecting transplanted stem cells in the treatment of cerebral ischemia according to journal (Table 9)

Table 9 Top 10 journals that published papers relating to the application of MRI for detecting transplanted stem cells in the treatment of cerebral ischemia included in Web of Science from 2002 to 2011

Journal	ISSN	Impact factor	Number of paper	% of total publication
Neuroimage	1053-8119	5.937	9	11.39
Stroke	0039-2499	5.756	8	10.13
Brain Research	0006-8993	2.623	5	6.33
Journal of Cerebral Blood Flow and Metabolism	0271-678X	4.522	5	6.33
Experimental Neurology	0014-4886	4.436	3	3.80
Journal of Neuroscience Research	0360-4012	2.958	3	3.80
Journal of the Neurological Sciences	0022-510X	2.167	2	2.53
Magnetic Resonance in Medicine	0740-3194	3.268	2	2.53
Neural Regeneration Research	1673-5374	0.180	2	2.53
NMR in Biomedicine	0952-3480	3.064	2	2.53

As seen in Table 9, most of the papers relating to the application of MRI for detecting transplanted stem cells in the treatment of cerebral ischemia appeared in *Neuroimage*, followed by *Stroke* and *Brain Research*.

Distribution of publications relating to the application of MRI for detecting transplanted stem cells in the treatment of cerebral ischemia according to country and institution

The USA published the highest number of papers (40, 50.63%). Japan ranked second (13, 16.46%), Germany ranked third (11). Sapporo Medical University, Oakland University, and Yale University were the three most productive institutions in terms of publishing papers relating to the application of MRI for detecting transplanted stems cells in the treatment of cerebral ischemia.

The most-cited papers from researchers at Sapporo Medical University from 2002 to 2011 were:

BDNF gene-modified mesenchymal stem cells promote functional recovery and reduce infarct size in the rat middle cerebral artery occlusion model[28], by Kurozumi K,

et al., published in *Molecular Therapy* in 2004, with 125 citations.

Intravenous infusion of immortalized human mesenchymal stem cells protects against injury in a cerebral ischemia model in adult rat[29], by Honma T, *et al.,* published in *Experimental Neurology* in 2006, with 80 citations.

Intravenous administration of glial cell line-derived neurotrophic factor gene-modified human mesenchymal stem cells protects against injury in a cerebral ischemia model in the adult rat[30], by Horita Y, *et al*., published in *Journal of Neuroscience Research* in 2006, with 72 citations.

Therapeutic benefits by human mesenchymal stem cells (hMSCs) and Ang-1 gene-modified hMSCs after cerebral ischemia[31], by Onda T, *et al*., published in *Journal of Cerebral Blood Flow and Metabolism* in 2008, with 52 citations.

The most cited relevant papers from Oakland University were:

In vivo magnetic resonance imaging tracks adult neural progenitor cell targeting of brain tumor[32], by Zhang Z, *et al.,* published in *Neuroimage* in 200, with citations.

Neurogenesis, angiogenesis, and MRI indices of functional recovery from stroke[33], by Chopp M, published in *Stroke* in 2007, with 58 citations.

Effects of administration route on migration and distribution of neural progenitor cells transplanted into rats with focal cerebral ischemia, an MRI study[34], by Li L, *et al.,* published in *Journal of Cerebral Blood Flow and Metabolism* in 2010, with 10 citations.

The most cited relevant papers from Yale University were:

Therapeutic benefits of angiogenetic gene-modified human mesenchymal stem cells after cerebral ischemia[35], by Toyama K, *et al.,* published in *Experimental Neurology* in 2009, with 31 citations.

Optimization of a therapeutic protocol for intravenous injection of human mesenchymal stem cells after cerebral ischemia in adult rats[36], by Omori Y, *et al*., published in *Brain Research* in 2008, with 15 citations.

DISCUSSION

The results of the current bibliometric study showed several research trends in terms of the application of MRI for monitoring stem cells transplantation. First, a total of 1 498 publications relating to the application of MRI for detecting transplanted stem cells were identified in Web of Science from 2002 to 2011, 382 of which regarding MRI for detecting transplanted SPIO-labeled stem cells and only 13 publications focus on application of MRI for detecting transplanted SPIO-labeled stem cells in the treatment of cerebral ischemia. The number of papers published annually has increased since 2002, indicating an increasing global interest in this topic over the last 10 years. Second, most relevant articles were published in Magnetic Resonance in Medicine. Finally, most articles on this topic were published in the USA.

In conclusion, the USA is the most productive country in terms of research into the application of MRI for tracking the progress of stem cell transplantation, while China ranked second for publications on the use of MRI for detecting SPIO-labeled stem cells, and fourth in relation to papers on MRI for detecting transplanted stem cells in the treatment of cerebral ischemia. The findings of this study demonstrated that few experimental studies have been investigated the use of MRI for tracking SPIO-labeled human UCB-MSCs during the treatment of cerebral ischemia.

Author contributions: Xianglin Zhang retrieved the references, extracted the data, conceived and designed the study, and Gang Wang wrote the manuscript. Furen Dong conceived and designed the study. Zhiming Wang contributed to the review, conception and design, paper revision, and study instruction.
Conflicts of interest: None declared.

REFERENCES

[1] Chang YC, Shyu WC, Lin SZ, et al. Regenerative therapy for stroke. Cell Transplant. 2007;16(2):171-181.
[2] Bang OY, Lee JS, Lee PH, et al. Autologous mesenchymal stem cell transplantation in stroke patients. Ann Neurol. 2005;57(6):874-882.
[3] Kraitchman DL, Gilson WD, Lorenz CH. Stem cell therapy: MRI guidance and monitoring. J Magn Reson Imaging. 2008;27(2):299-310.
[4] Weissleder R. Molecular imaging: exploring the next frontier. Radiology. 1999;212(3):609-614.
[5] Bulte JW, Douglas T, Witwer B, et al. Monitoring stem cell therapy in vivo using magnetodendrimers as a new class of cellular MR contrast agents. Acad Radiol. 2002; 9(2): S332-335.
[6] Sehoefer R, KeMbach R, Wiskirchen J, et al. Transferrin respector upregulation: in vitro labeling of rat mesenchymal stem cells with superparamagnetic iron oxide. Radiology. 2007;244(2):514-523.
[7] Frank JA, Zywicke H, Jordan EK, et al. Magnetic intracellular labeling of mammalian cells by combining (FDA-approved) superparamagnetic iron oxide MR contrast agents and commonly used transfection agents. Acad Radiol. 2002;9(2):S484-487.
[8] Arbab AS, Bashaw LA, Miller BR, et al. Characterization of biophysical and metabolic properties of cells labeled with superparamagnetie iron oxide nanoparticles and transfection agent for cellular MR imaging. Radiology. 2003; 229(3):838-846.

[9] Arbab AS. Yoeum GT, Wilson LB, et al. Comparison of transfection agents in forming complexes with ferumoxides, cell labeling efficiency, and cellular viability. Mol Imaging. 2004;3(1):24-32
[10] Norman AB, Thomas SR, Pratt RG, et al. Magnetic resonance imaging of neural transplants in rat brain using a superparamagnetic contrast agent. Brain Res. 1992; 594(2):279-283.
[11] Stoll G, Wesemeier C, Gold R, et al. In vivo monitoring of macro-phage infiltration in experimental autoimmune neuritis by magneticresonance imaging. J Neuroimmunol. 2004;149(1-2):142-146.
[12] Chen ZC, Xu RX, Yang ZJ, et al. Sinerem labeling and MRI tracking of neural stem cells in vivo and in vitro. Nanfang Yike Daxue Xuebao. 2007;27(5):611-615.
[13] Chung DJ, Choi CB, Lee SH, et al. Intraarterially delivered human umbilical cord blood-derived mesenchymal stem cells in canine cerebral ischemia. J Neurosci Res. 2009; 87(16):3554-3567.
[14] Wollert KC, Meyer GP, Lotz J, et al. Intracoronary autologous bone-marrow cell transfer after myocardial infarction: the BOOST randomised controlled clinical trial. Lancet. 2004;364(9429):141-148.
[15] Bjorklund LM, Sánchez-Pernaute R, Chung S, et al. Embryonic stem cells develop into functional dopaminergic neurons after transplantation in a Parkinson rat model. Proc Natl Acad Sci U S A. 2002;99(4): 2344-2349.
[16] Lunde K, Solheim S, Aakhus S, et al. Intracoronary injection of mononuclear bone marrow cells in acute myocardial infarction. N Engl J Med. 2006 ;355(12): 1199-1209.
[17] Schächinger V, Assmus B, Britten MB, et al. Transplantation of progenitor cells and regeneration enhancement in acute myocardial infarction: final one-year results of the TOPCARE-AMI Trial. J Am Coll Cardiol. 2004;44(8):1690-1699.
[18] Corot C, Robert P, Idée JM, et al. Recent advances in iron oxide nanocrystal technology for medical imaging. Adv Drug Deliv Rev. 2006;58(14):1471-1504.
[19] Hoehn M, Küstermann E, Blunk J, et al. Monitoring of implanted stem cell migration in vivo: a highly resolved in vivo magnetic resonance imaging investigation of experimental stroke in rat. Proc Natl Acad Sci U S A. 2002;99(25):16267-16272.
[20] Kraitchman DL, Heldman AW, Atalar E, et al. In vivo magnetic resonance imaging of mesenchymal stem cells in myocardial infarction. Circulation. 2003;107(18): 2290-2293.
[21] de Vries IJ, Lesterhuis WJ, Barentsz JO, et al. Magnetic resonance tracking of dendritic cells in melanoma patients for monitoring of cellular therapy. Nat Biotechnol. 2005; 23(11):1407-1413.
[22] Bulte JW, Kraitchman DL. Iron oxide MR contrast agents for molecular and cellular imaging. NMR Biomed. 2004;17(7):484-499.
[23] Frank JA, Miller BR, Arbab AS, et al. Clinically applicable labeling of mammalian and stem cells by combining superparamagnetic iron oxides and transfection agents. Radiology. 2003;228(2):480-487.
[24] Arbab AS, Bashaw LA, Miller BR, et al. Characterization of biophysical and metabolic properties of cells labeled with superparamagnetic iron oxide nanoparticles and transfection agent for cellular MR imaging. Radiology. 2003;229(3):838-846.
[25] Lu CW, Hung Y, Hsiao JK, et al. Bifunctional magnetic silica nanoparticles for highly efficient human stem cell labeling. Nano Lett. 2007;7(1):149-154.
[26] Bulte JW, Duncan ID, Frank JA. In vivo magnetic resonance tracking of magnetically labeled cells after transplantation. J Cereb Blood Flow Metab. 2002;22(8): 899-907.
[27] Kostura L, Kraitchman DL, Mackay AM, et al. Feridex labeling of mesenchymal stem cells inhibits chondrogenesis but not adipogenesis or osteogenesis. NMR Biomed. 2004;17(7):513-517.
[28] Kurozumi K, Nakamura K, Tamiya T, et al. BDNF gene-modified mesenchymal stem cells promote functional recovery and reduce infarct size in the rat middle cerebral artery occlusion model. Mol Ther. 2004; 9(2):189-197.
[29] Honma T, Honmou O, Iihoshi S, et al. Intravenous infusion of immortalized human mesenchymal stem cells protects against injury in a cerebral ischemia model in adult rat. Exp Neurol. 2006;199(1):56-66.
[30] Horita Y, Honmou O, Harada K, et al. Intravenous administration of glial cell line-derived neurotrophic factor gene-modified human mesenchymal stem cells protects against injury in a cerebral ischemia model in the adult rat. J Neurosci Res. 2006;84(7):1495-1504.
[31] Onda T, Honmou O, Harada K, et al. Therapeutic benefits by human mesenchymal stem cells (hMSCs) and Ang-1 gene-modified hMSCs after cerebral ischemia. J Cereb Blood Flow Metab. 2008;28(2):329-340.
[32] Zhang Z, Jiang Q, Jiang F, et al. In vivo magnetic resonance imaging tracks adult neural progenitor cell targeting of brain tumor. Neuroimage. 2004;23(1): 281-287.
[33] Chopp M, Zhang ZG, Jiang Q. Neurogenesis, angiogenesis, and MRI indices of functional recovery from stroke. Stroke. 2007;38(2 Suppl):827-831.
[34] Li L, Jiang Q, Ding G, et al. Effects of administration route on migration and distribution of neural progenitor cells transplanted into rats with focal cerebral ischemia, an MRI study. J Cereb Blood Flow Metab. 2010;30(3):653-662.
[35] Toyama K, Honmou O, Harada K, et al. Therapeutic benefits of angiogenetic gene-modified human mesenchymal stem cells after cerebral ischemia. Exp Neurol. 2009;216(1):47-55.
[36] Omori Y, Honmou O, Harada K, et al. Optimization of a therapeutic protocol for intravenous injection of human mesenchymal stem cells after cerebral ischemia in adult rats. Brain Res. 2008;1236:30-38.

(Edited by Zhao LJ/Song LP)