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Use of stem cell transplantation to treat epilepsy

A Web of Science-based literature analysis

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Abstract

OBJECTIVE: To identify global research trends in the use of stem cell transplantation to treat epilepsy.

DATA RETRIEVAL: We performed a bibliometric analysis of studies on the use of stem cell transplantation to treat epilepsy during 2002–2011, retrieved from Web of Science, using the key words epilepsy or epileptic or epilepticus or seizure and “stem cell”.

SELECTION CRITERIA: Inclusion criteria: (a) peer-reviewed published articles on the use of stem cell transplantation to treat epilepsy indexed in Web of Science; (b) original research articles, reviews, meeting abstracts, proceedings papers, book chapters, editorial material, and news items.

MAIN OUTCOME MEASURES: (a) Annual publication output; (b) type of publication; (c) publication by research field; (d) publication by journal; (e) publication by author; (f) publication by country and institution; (g) publications by institution in China; (h) most-cited papers; and (i) papers published by Chinese authors or institutions.

RESULTS: A total of 460 publications on the use of stem cell transplantation to treat epilepsy were retrieved from Web of Science, 2002–2011. The number of publications gradually increased over the 10-year study period. Articles and reviews constituted the major types of publications. More than half of the studies were in the field of neuroscience/neurology. The most prolific journals for this topic were *Epilepsia*, *Bone Marrow Transplantation*, and *Journal of Neuroscience*. Of the 460 publications, almost half came from American authors and institutions; relatively few papers were published by Chinese authors or institutions.

CONCLUSION: Literature on stem cell transplantation for epilepsy includes many reports of basic research, but few of clinical trials or treatments. Exact effects are not yet evaluated. Epilepsy rehabilitation is a long-term, complex, and comprehensive system engineering. With advances in medical development, some effective medical, social and educational measures are needed to facilitate patient’s treatment and training and accelerate the recovery of life ability, learning ability and social adaptability to the largest extent to improve patient’s quality of life.

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Key Words

epilepsy; seizure; hippocampus; stem cell; ancestral cell; neurons; neurogenesis; central nervous system; brain; bibliometric; neural regeneration

Research Highlights

(1) We performed a bibliometric analysis of studies published during 2002–2011 retrieved from Web of Science on the use of stem cell transplantation to treat epilepsy.
(2) We analyzed the publication year, types, research fields, journals, authors, countries, and institutions.
(3) We especially analyzed the publication patterns of Chinese institutions to provide information on research status in China.

Abbreviations

TLE, temporal lobe epilepsy; FLE, frontal lobe epilepsy; PLE, parietal lobe epilepsy; OLE, occipital lobe epilepsy; GE, generalized epilepsy

INTRODUCTION

Epilepsy is a chronic brain dysfunction syndrome with a variety of causes. This paroxysmal, transient cerebral dysfunction is caused by repeated oversynchronous discharge of brain nerve cell populations[1-3]. Seizures may induce intense change to internal and external environment of brain cells, causing brain damage, brain cell degeneration and necrosis.

With medical model transform from simple biomedical mode to biological-psychological-social medical mode, quality of life has been paid increasing attention because it has been widely used for evaluation of patient's well-beings and disease rehabilitation. For this reason, epilepsy rehabilitation should take patient's quality of life into account in addition to onset control and symptom relief.

Although epilepsy has many treatments, such as medication, surgery, physical therapy and psychotherapy, these treatments do not cure epilepsy and can only control seizures. Stem cell transplantation has shown great potential in reconstructing nervous system function in animal models of neurodegeneration, and in humans with Parkinson's disease[4-5], and could conceivably rebuild function and improve prognoses of patients with epilepsy. The mechanism of stem cell transplantation would involve stem cells implanted into the brain to repair or replace damaged or denatured neurons and glial cells, and rebuild synapses or secrete neurotransmitters to regulate neural function, alleviate symptoms, and ameliorate nervous system defects. Studies have shown that stem cell transplantation promotes release of inhibitory neurotransmitters, thereby restraining seizures[6-7].

In this study, we analyzed the research trends in the use of stem cell transplantation to treat epilepsy, based on a bibliometric analysis of papers in Web of Science, 2002–2011.

DATA SOURCES AND METHODOLOGY

Data retrieval

This study used bibliometric analyses to quantitatively and qualitatively investigate research trends in studies of stem cell transplantation to treat epilepsy. We searched Web of Science, a research database of publications and citations selected and evaluated by the Institute for Scientific Information in Philadelphia, PA, USA, using the key words epilepsy or epileptic or epilepticus or seizure and "stem cell". We limited the period of publication from 2002 to 2011, and compiled a bibliography of all articles related to stem cell transplantation for epilepsy. We downloaded the data on August 20, 2012.

Inclusion criteria

The inclusion criteria were: (1) published peer-reviewed articles on the use of stem cell transplantation to treat epilepsy, including original research articles, reviews, meeting abstracts, proceedings papers, book chapters, editorial material, and news items, which were indexed in Web of Science; (2) 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 several corrected papers from the total articles analyzed.

The outcomes of all articles referring to the use of stem cell transplantation to treat epilepsy were assessed using the following criteria: (a) publication by year; (b) type of publication; (c) research field; (d) journal; (e) authors; (f) country and institution; (g) institutions specifically in China; (h) most-cited papers; and (i) papers published by Chinese authors or institutions.

RESULTS

Output by year of publications relating to stem cell transplantation for epilepsy in Web of Science, 2002–2011

A total of 460 publications on stem cell transplantation for epilepsy were retrieved from Web of Science, 2002–2011. The number of relevant publications gradually increased over the 10-year study period, with 13 papers published and included in Web of Science in 2002, increasing to 81 in 2010. Numbers of papers published slightly decreased in 2005, 2006, 2009 and 2011 (Figure 1).

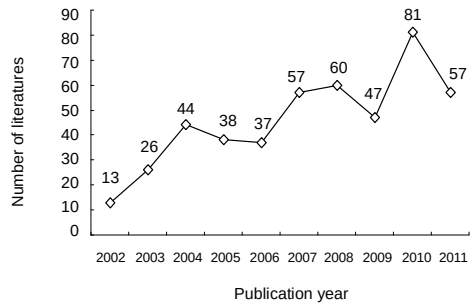

Figure 1 Output by year of publications on stem cell transplantation for epilepsy in Web of Science, 2002–2011.

Different types of publications relating to stem cell transplantation for epilepsy, 2002–2011

Articles and reviews constituted the major types of publications related to stem cell transplantation for epilepsy over this period (Table 1), with 317 articles (68.9%) and 99 reviews (21.5%). The other types are meeting abstracts, proceedings papers, editorial material, letters, and book chapters.

Table 1 Type of publications on stem cell transplantation for epilepsy included in Web of Science, 2002–2011

Type of literature	No. of papers	% of total publications
Article	317	68.913
Review	99	21.522
Meeting abstract	27	5.870
Proceedings paper	15	3.261
Editorial material	8	1.739
Letter	4	0.870
Book chapter	1	0.217

Distribution by research field in publications on stem cell transplantation for epilepsy in Web of Science, 2002–2011 (Figure 2)

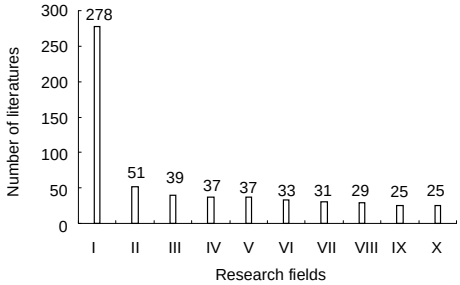

Figure 2 Distribution by research field for publications on stem cell transplantation for epilepsy in Web of Science, 2002–2011.

I: Neurosciences neurology; II: Hematology; III: Oncology; IV: Biochemistry molecular biology; V: Pharmacology pharmacy; VI: Surgery; VII: Transplantation; VIII: Immunology; IX: Cell biology; X: Pediatrics.

Among the research fields represented in publications relating to the use of stem cell transplantation for epilepsy in Web of Science, 2002–2011, 278 papers were in the field of neuroscience/neurology. The second best-represented field, with 51 papers, was hematology. In the fields of oncology, biochemistry molecular biology, pharmacology pharmacy, surgery, and transplantation, more than 30 papers on stem cell transplantation for epilepsy were published.

Output by journal of publications on stem cell transplantation for epilepsy in Web of Science, 2002–2011 (Figure 3)

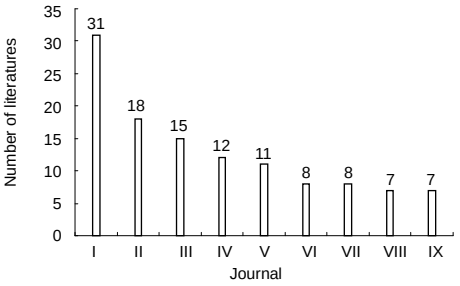

Figure 3 Top nine journals for publications on stem cell transplantation for epilepsy between 2002 and 2011.

I: *Epilepsia*; II: *Bone Marrow Transplantation*; III: *Journal of Neuroscience*; IV: *European Journal of Neuroscience*; V: *Neurosurgery*; VI: *Journal of Neuroscience Research*; VII: *Neurobiology of Disease*; VIII: *Epilepsy Research*; IX: *Neuroscience*.

In the period of interest, *Epilepsia* published 31 papers, followed by *Bone Marrow Transplantation* and *Journal of Neuroscience*, which published 18 and 15 papers, respectively. The other six top journals are *European Journal of Neuroscience*, *Neurosurgery*, *Journal of Neuroscience Research*, *Neurobiology of Disease*, *Epilepsy Research* and *Neuroscience.*

Distribution by author for publications on stem cell transplantation for epilepsy in Web of Science, 2002–2011

Detlev Boison has published 22 papers (4.8%) on stem cell transplantation for epilepsy—much more than any other author (Table 2). Ashok K. Shetty ranked second with 17 papers (3.7%), and Bharathi Hattiangady ranked third with 12 papers (2.6%).

Detlev Boison's paper, "The adenosine kinase hypothesis of epileptogenesis", was cited 74 times[5]; another paper, "Suppression of kindling epileptogenesis by adenosine releasing stem cell-derived brain implants", was cited 64 times[8].

Ashok K. Shetty's paper, "Efficacy of doublecortin as a marker to analyze the absolute number and dendritic

growth of newly generated neurons in the adult dentate gyrus", was cited 305 times[9]; another paper, "Chronic temporal lobe epilepsy is dentate neurogenesis in the adult associated with severely declined hippocampus", was cited 98 times[10] (Table 2).

Table 2 Authors publishing papers on stem cell transplantation for epilepsy included in Web of Science, 2002–2011

Author	No. of papers	% of total publications
Detlev Boison	22	4.783
Ashok K. Shetty	17	3.696
Bharathi Hattiangady	12	2.609
Jack M. Parent	9	1.957
Iver A. Langmoen	8	1.739
Paul Boon	7	1.522
Oliver Bruestle	7	1.522
Kon Chu	7	1.522
William P. Gray	7	1.522
Keun-Hwa Jung	7	1.522
Robrecht Raedt	7	1.522
Mahendra S. Rao	7	1.522

Bharathi Hattiangady's paper, "Chronic temporal lobe epilepsy is dentate neurogenesis in the adult associated with severely declined hippocampus", was cited 98 times[10], this information is repeated from the paragraph above; another paper, "Concise review: Prospects of stem cell therapy for temporal lobe epilepsy", was cited 40 times[11].

Output by country and institution of publications on stem cell transplantation for epilepsy in Web of Science, 2002–2011 (Figures 4, 5)

Analysis of contributions of different countries/states to publications was based on journal articles in which the address and affiliation of at least one author were provided. A total of 460 articles were analyzed by country and institution. Most papers on stem cell transplantation for epilepsy were published in the USA (186 papers), followed by Germany (47 papers) and Japan (40 papers) (Figure 4). China published 12 papers, ranking the 11th. Duke University, the University of California system and Veterans Affairs Medical Center were the most prolific research institutes (Figure 5). Six of the top 14 research institutes publishing in this field were in the USA.

Distribution by institution in China for publications on stem cell transplantation for epilepsy in Web of Science, 2002–2011

Chongqing Medical University and Harbin Medical University were the most prolific research institutes in China for the publication of papers on stem cells transplantation for epilepsy in Web of Science, 2002–2011 (Table 3). Although they each published two papers, we found that only a few papers were published by Chinese authors or institutions in this area.

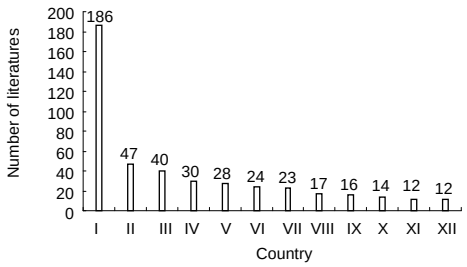

Figure 4 The top 12 countries publishing papers on stem cell transplantation for epilepsy, 2002–2011.

I: USA; II: Germany; III: Japan; IV: England; V: Italy; VI: France; VII: Sweden; VIII: Canada; IX: South Korea; X: Brazil; XI: China; XII: Switzerland.

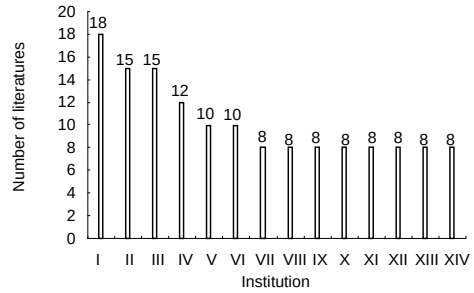

Figure 5 The top 14 institutes publishing papers on stem cell transplantation for epilepsy, 2002–2011.

I: Duke University, USA; II: University of California system, USA; III: Veterans Affairs Medical Center, USA; IV: University of Bonn, Germany; V: Harvard University, USA; VI: University of Michigan, USA; VII: Ege University, India; VIII: Lund University, Sweden; IX: Okayama University, Japan; X: Seoul National University, Korea; XI: University of Amsterdam, Netherlands; XII: Federal University of Santa Maria, Brazil; XIII: University of Oslo, Norway; XIV: Yale University, USA.

Table 3 Chinese institutions publishing papers on stem cell transplantation for epilepsy, 2002–2011

Institution	No. of papers	% of total publications
Chongqing Medical University	2	16.667
Harbin Medical University	2	16.667
Capital Medical University	1	8.333
Central South University	1	8.333
Chinese Academy of Sciences	1	8.333
Fujian Medical University	1	8.333
Shanghai Jiao Tong University	1	8.333
Shanghai Research Center for Model Organisms	1	8.333
Shanghai University	1	8.333
Third Military Medical University	1	8.333
Tongji University	1	8.333
Zunyi Medical College	1	8.333

Highly cited papers on stem cell transplantation for epilepsy in Web of Science, 2002–2011

Of the 460 papers on stem cell transplantation for epilepsy cited in Web of Science, 2002–2011, the 2005 paper, "Adult neurogenesis: From precursors to network and physiology"[12], was cited 401 times, which was more times than any other paper. It was published by *Physiological Reviews.*

Of the 15 most-cited papers, three were published in *European Journal of Neuroscience*, three in *Journal of Neuroscience*, and the remaining nine were published in nine different journals.

Of the 15 most-cited papers, three each were published in 2003 and 2004, two each were in 2002, 2005, 2006 and 2009 and one was in 2007 (Table 4).

Papers on stem cell transplantation for epilepsy published by Chinese authors or institutions in Web of Science, 2002–2011 (Table 5)

A total of 12 papers on stem cell transplantation for epilepsy published by Chinese authors or institutions were cited in Web of Science, 2002–2011 (Table 5).

The 2010 paper, "Activation of ERK by spontaneous seizures in neural progenitors of the dentate gyrus in a mouse model of epilepsy"[26], published by *Experimental Neurology*; and the 2010 paper "Tacrolimus-associated posterior reversible encephalopathy syndrome after solid organ transplantation"[27], published by *European Neurology,* were both cited seven times—more times than any other paper in this group. Of the 12 papers, six were published in 2010, two each were published in 2009 and 2011, and one each was published in 2006 and 2007.

Table 4 The 15 top-cited papers on stem cell transplantation for epilepsy in Web of Science, 2002–2011

Title	Author	Journal	Publication year	Total citation	Average per year
Adult neurogenesis: from precursors to network and physiology[12]	Abrous DN, *et al.*	*Physiological Reviews*	2005	401	50.12
Doublecortin expression levels in adult brain reflect neurogenesis[13]	Couillard-Despres S, *et al*.	*European Journal of Neuroscience*	2005	305	38.12
Efficacy of doublecortin as a marker to analyse the absolute number anddendritic growth of newly generated neurons in the adult dentate gyrus[9]	Rao MS, *et al*.	*European Journal of Neuroscience*	2004	305	33.89
Sox2 deficiency causes neurodegeneration and impaired neurogenesis in the adult mouse brain[14]	Ferri AL, *et al.*	*Development*	2004	196	21.78
Neural stem cell proliferation is decreased in schizophrenia, but not in depression[15]	Reif A, *et al*.	*Molecular Psychiatry*	2006	185	26.43
The role of neurotrophic factors in adult hippocampal neurogenesis, antidepressant treatments and animal models of depressive-like behavior[16]	Schmidt HD, *et al*.	*Behavioural Pharmacology*	2007	183	30.50
Mood stabilizer valproate promotes ERK pathway-dependent cortical neuronal growth and neurogenesis[17]	Hao Y, *et al*.	*Journal of Neuroscience*	2004	175	19.44
Gene profile of electroconvulsive seizures: induction of neurotrophic and angiogenic factors[18]	Newton SS, *et al*.	*Journal of Neuroscience*	2003	166	16.60
Injury-induced neurogenesis in the adult mammalian brain[19]	Parent JM	*Neuroscientist*	2003	157	15.70
Brain inflammation and adult neurogenesis: the dual role of microglia[20]	Ekdahl CT, *et al*.	*Neuroscience*	2009	144	36.00
Adult-born hippocampal neurons mature into activity-dependent responsiveness[21]	Jessberger S, *et al*.	*European Journal of Neuroscience*	2003	140	14.00
Cation-chloride cotransporters and neuronal function [22]	Blaesse P, *et al.*	*Neuron*	2009	136	34.00
Regulation of adult hippocampal neurogenesis - implications for novel theories of major depression[23]	Kempermann G	*Bipolar Disorders*	2002	133	12.09
Gangliogliomas: an intriguing tumor entity associated with focal epilepsies[24]	Blümcke I, *et al*.	*Journal of Neuropathology and Experimental Neurology*	2002	117	10.64
Tumor necrosis factor receptor 1 is a negative regulator of progenitor proliferation in adult hippocampal neurogenesis[25]	Iosif RE, *et al*.	*Journal of Neuroscience*	2006	110	15.71

Table 5 Papers on stem cell transplantation for epilepsy from Chinese authors or institutions, 2002–2011

Title	Author	Journal	Publication year	Total citation	Average per year
Activation of ERK by spontaneous seizures in neural progenitors of the dentate gyrus in a mouse model of epilepsy[26]	Li Y, *et al*.	*Experimental Neurology*	2010	7	2.33
Tacrolimus-associated posterior reversible encephalopathy syndrome after solid organ transplantation[27]	Wu Q, *et al*.	*European Neurology*	2010	7	2.33
The combined therapy of intrahippocampal transplantation of adult neural stem cells and intraventricular erythropoietin-infusion ameliorates spontaneous recurrent seizures by suppression of abnormal mossy fiber sprouting[28]	Jing M, *et al*.	*Brain Research*	2009	5	1.25
Long-term antiepileptic drug administration during early life inhibits hippocampal neurogenesis in the developing brain[29]	Chen J, *et al*.	*Journal of Neuroscience Research*	2009	5	1.25
Involvement of over-expressed BMP4 in pentylenetetrazol kindling-induced cell proliferation in the dentate gyrus of adult rats[30]	Yin J, *et a*l.	*Biochemical and Biophysical Research Communications*	2007	5	0.83
bFGF and heparin but not laminin are necessary factors in the mediums that affect NSCs differentiation into cholinergic neurons[31]	Ren W, *et al*.	*Neurological Research*	2006	4	0.57
HHV-6 encephalitis in pediatric unrelated umbilical cord transplantation: a role for ganciclovir prophylaxis?[32]	Cheng FW, *et al.*	*Pediatric Transplantation*	2010	3	1.00
Hippocampal stem cell grafting-mediated recovery of injured hippocampus in the rat model of temporal lobe epilepsy[33]	Shen H, *et al*.	*International Journal of Neuroscience*	2010	1	0.33
Evidence of endothelial progenitor cells in the human brain and spinal cord arteriovenous malformations[34]	Gao P, *et al.*	*Neurosurgery*	2010	1	0.33
Transplantation of neural stem cells overexpressing cardiotrophin-1 inhibits sprouting of hippocampal mossy fiber in a rat model of status epilepticus[35]	Shu X, *et al.*	*Cell Biochemistry and Biophysics*	2011	0	0.00
Neural stem cell activation and glial proliferation in the hippocampal CA3 region of posttraumatic epileptic rats[36]	Lin YX, *et al.*	*Neural Regeneration Research*	2011	0	0.00
Identification of a Smad4/YY1-recognized and BMP2-responsive transcriptional regulatory module in the promoter of mouse GABA transporter subtype I (Gat1) Gene[37]	Yao M, *et al.*	*Journal of Neuroscience*	2010	0	0.00

DISCUSSION

In this bibliometric analysis based on Web of Science, the number of publications gradually increased over the 10-year study period; most were articles and reviews. The most prolific journals in this area are *Epilepsia*, *Bone Marrow Transplantation*, and *Journal of Neuroscience*. Of the 460 publications retrieved from Web of Science, 2002–2011, almost half came from American authors and institutions. However, only a few papers were published by Chinese authors or institutions.

There are several subtopics that need to be addressed regarding stem cell transplantation for epilepsy. First, cell viability issues include directed differentiation *in vivo*, functional integration, possible formation of tumors, and rejection reaction. Second, sources of stem cells constitute another set of problems. Third, cell therapy based on embryonic cells have a significant obstacle, *i.e*. the cells' tendency to remain closely spaced at the graft site core[38-42]. Fourth, we need to learn more about how stem cells differentiate into neurons of specific areas, cell signaling pathways inside and outside glial cells, and their physiological and biochemical characteristics. This could help induce and direct stem cell differentiation, ideally leading to the particular cell types most likely to produce antiepileptic function[43-47].

Although much basic research is reported in the literature, few reports describe clinical treatments or trials. Of those that do report clinical applications, patient follow-up tends to be short or underdescribed. Exact effects of this therapy have yet to be adequately evaluated by multiple medical research centers through evidence-based medicine.

Epilepsy rehabilitation is a long-term, complex, and comprehensive system engineering. With advances in medical development, some effective medical, social and educational measures are added to facilitate patient's treatment and training and accelerate the recovery of life ability, learning ability and social adaptability to the largest extent to improve patient's quality of life. For

epilepsy rehabilitation, control of disease onset is a key link. A combined method of traditional Chinese medicine and western medicine has a synergistic effect and can significantly strength the therapeutic effects and reduce the dose use and adverse events of western medicine. Nevertheless, how to select drug kinds and how to match them needs further clinical investigation. Noninvasive physical methods, for example, massage, acupuncture and moxibustion and magnetic stimulation therapy, also greatly improve patient's quality of life and deserve further investigation.

Author contributions: Zhongmin Yin retrieved the references, extracted the data, conceived and designed the study, and wrote the manuscript. Yushu Dong retrieved the references, extracted the data, and conceived and designed the study. Jiyang Zhang and Li Wang contributed to the review, conception and design, paper revision, and study instruction.
Conflicts of interest: None declared.
Author statements: The manuscript is original, has not been submitted to or is not under consideration by another publication, has not been previously published in any language or any form, including electronic, and contains no disclosure of confidential information or authorship/ patent application disputations.

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