Stem cell transplantation for treating stroke: status, trends and development

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Abstract
The developing approaches of thrombolytic therapy, endovascular treatment, neuroprotective therapy, and stem cell therapy have enabled breakthroughs in stroke treatment. In this study, we summarize and analyze trends and progress in stem cell transplantation for stroke treatment by retrieval of literature from Thomson Reuters Web of Science database, the NIH Clinical Trial Planning Grant Program, and Clinical Trials Registration Center in North America. In the last 10 years, there has been an increasing number of published articles on stem cell transplantation for stroke treatment. In particular, research from the USA and China has focused on stem cell transplantation. A total of 2,167 articles addressing stem cell transplantation for stroke treatment from 2004 to 2013 were retrieved from the Thomson Reuters Web of Science database. The majority of these articles were from the USA (854, 39.4%), with the journal Stroke publishing the most articles (145, 6.7%). Of the published articles, 143 were funded by the National Institutes of Health (accounting for 6.6% of total publications), and 91 by the National Natural Science Foundation of China. Between 2013 and 2014, the National Institutes of Health provided financial support ($130 million subsidy) for 329 research projects on stroke therapy using stem cell transplantation. In 2014, 215 new projects were approved, receiving grants of up to $70,440,000. Ninety clinical trials focusing on stem cell transplantation for stroke were registered in the Clinical Trial Registration Center in North America, with 40 trials registered in the USA (ranked first place). China had the maximum number of registered research or clinical trials (10 projects).

Key Words: nerve regeneration; stem cell; stroke; transplantation; neural stem cell; bone marrow mesenchymal stem cell; umbilical cord blood stem cell; embryonic stem cell; neural regeneration

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Introduction
Stroke is the collective name for cerebrovascular disease with brain functional deficits due to a number of causes. Stroke is associated with high morbidity, mortality, and disability rates, and is regarded as one of three major lethal diseases in most countries because of increasing morbidity and mortality (Bliss et al., 2007; Li et al., 2009). Stem cell transplantation offers a new avenue for stroke treatment, and has been used to treat stroke for the last 10 years (Kalluri et al., 2008). Stem cells are used to replace necrotic nerve tissue, and thereby contribute to neural network reconstruction through a number of mechanisms, including replacing necrotic neurons with new functional neurons, maintaining neural circuits and reconstructing neural conduction pathways by replacing necrotic glial cells, providing nutrients for tissue at the peri-infarct penumbra, and promoting survival, transfer, and differentiation of endogenous progenitors through neurotrophic factor secretion. After transplantation, both endogenous and exogenous neural stem cells migrate to the distal injury area and differentiate into new nerve cells, promoting tissue restoration and functional restoration in the central nervous system, particularly after cerebral infarction (Thored et al., 2006; Zheng et al., 2009). A variety of stem cells have been used in stroke treatment, including neural, bone marrow mesenchymal, umbilical cord blood, and embryonic stem cells (Darsalia et al., 2005; Liu, 2013). Although these stem cells are derived from different cell types, they share a similar theoretical basis in treatment of ischemic stroke, namely cell replacement, immunomodulation, neuroprotection, and neurotrophism, which contribute to relieving nerve damage and promoting functional recovery (Hasegawa et al., 2006; Sensebé et al., 2010). The mode of transplantation is one component of efficient stem cell transplantation for stroke treatment, and commonly used approaches involve direct, intravenous, or arterial injections. Moreover, the choice of stem cells (neural, bone marrow mesenchymal, umbilical cord blood or embryonic) is also key to stem cell transplantation (Darsalia et al., 2007). Efficacy of stroke treatment using stem cells is determined by the stem cell source, transplantation approach, stem cell survival and host integration, and treatment safety (Arvidsson et al., 2002; Ourednik et al., 2002), although many questions are unanswered: how can stem cell transplantation success in clinical practice be achieved in a safe and rapid manner based on current clinical trial results? And what are the mechanisms of action? Further efforts are needed to explore treatment profiles (Zhao et al., 2002; Kawai et al., 2010). In this study, we analyzed published literature on stroke stem cell transplantation by examining funded and registered studies.
Trends from Published Articles about Stem Cell Transplantation for Stroke Treatment

Computer-based retrieval was performed using Thomson Reuters Web of Science database (http://webofknowledge.com/), the National Institutes of Health (NIH) Common Fund database (http://www.nih.gov/), and Clinical Trial Registration Center in North America (http://www.clinicaltrials.gov/), between 2004-01-01 and 2013-12-31. Key words used were "stem cell", "stroke", "transplantation", "neural stem cells", "mesenchymal stem cells", "bone marrow mesenchymal stem cells", "bone mesenchymal stem cells", "adipose-derived stem cells", "umbilical cord blood stem cells", and "embryonic stem cell".

Inclusion criteria
Any article about stem cell transplantation for stroke treatment was included.

Exclusion criteria
(1) Articles without the authors' approval; and (2) unpublished articles.

Literature analysis
Included articles were quantitatively and qualitatively analyzed using the following categories: publication time, publication nation and region, article type, institution distribution, and publication sources. Analysis methods included retrieval from Web of Science and NIH Common Fund databases, analysis functions in the Clinical Trial Registration Center in North America, and graphics functions of Excel software. Article types included original research, reviews, conference abstracts, conference articles, editorials, and chapters.

Results

Efficacy of stem cell transplantation for stroke treatment
We initially compared the advantages and disadvantages of using different stem cell types for transplantation in stroke treatment (Table 1).

Literature analysis of the Web of Science database between 2004 and 2013

Number of articles on different stem cell types for stroke treatment
Next, we determined the number of articles published in the Web of Science database between 2004 and 2013, on different types of stem cell transplantation for stroke treatment (Table 2).

Of the included articles, those focusing on neural stem cell transplantation have sharply increased, followed by bone marrow stem cell transplantation. Articles about embryonic and umbilical cord blood stem cell transplantation do not show significant increases. In total, 2,617 related articles were assessed, including 87 articles published in 2004, 102 in 2005, 146 in 2006, 159 in 2007, 170 in 2008, 262 in 2009, 280 in 2010, 319 in 2011, 312 in 2012, and 388 in 2013. Therefore, the number of stroke treatment related articles published in the Web of Science database has increased within the last 5 years, with the maximum published in 2013.

Highly cited articles on stem cell transplantation for stroke treatment
According to bibliometrics, citation frequency is the main indicator for determining literature quality and reflects the academic value of peer reviews, with higher citation frequencies indicating greater scientific value (Zhou et al., 2005; Yue et al., 2008). Thus, we determined highly cited articles from the 2,617 related articles identified from the Web of Science database between 2004 and 2013 (Table 3).

Analysis of publication countries
Publication countries of included articles identified from the Web of Science database between 2004 and 2013 were analyzed (Figure 1).

Of the 2,167 published articles, the USA has published the most (854 articles, 39.4%), followed by China (361 articles), Japan (198 articles), Germany (173 articles), South Korea (157 articles), UK (120 articles), Canada (112 articles), and other countries (< 100 articles) (Figure 2). There are three Asian countries in the top nine, showing regional dominance in this research field.

Analysis of article type
The majority of articles published were original research (up to 1,535 articles, 70.8%), followed by reviews (395 articles, 18.3%), meeting abstracts (147 articles), and other types (< 100 articles) (Table 4).

Analysis of publication institutions
Publication institutions of included articles were analyzed (Figure 2).

Of the top ten institutions publishing articles on stem cell transplantation for stroke treatment, Oakland University occupies first place (83 articles, 3.8%), followed by the Henry Ford Hospital (77 articles), University of Florida (68 articles), and Stanford University (63 articles). The majority of publication institutions are located in the USA, although Fudan University and Asia University are also ranked in the top ten.

Analysis of publication journals
The majority of included articles were published in brain science journals, including Stroke (145 articles, 6.7%), Brain Research (72 articles), Cell Transplantation (70 articles), Journal of Cerebral Blood Flow and Metabolism (63 articles), PLOS ONE (57 articles), Experimental Neurology (51 articles), and other journals (< 50 articles) (Table 5). Statistical analysis of publication journals enables researchers and physicians to identify key journals and determine relevant literature on stem cell transplantation for stroke treatment. In turn this will guide submission and improve acceptance rates, which is conducive to expanding research achievements.

Analysis of funding agencies
The funding agencies responsible for published articles were determined (Table 6).
Table 1 Different stem cell types for stroke treatment

| Cell types                        | Advantages                                                                 | Disadvantages                                                                 |
|-----------------------------------|-----------------------------------------------------------------------------|-------------------------------------------------------------------------------|
| Neural stem cells                 | Neural stem cells can proliferate, differentiate, and migrate into the ischemic area, have strong capacity of restoration and high survival rate. | Neural stem cells have limited self-renewal and pluripotency capabilities in vitro. |
| Bone marrow mesenchymal stem cells| Bone marrow mesenchymal stem cells have pluripotent differentiation potential and easy access for harvesting and amplification; these cells are involved in endogenous neurogenesis. | The optimal transplantation approach and the number of transplanted cells need further exploration, as well as the assessment of transplantation efficacy and safety. |
| Embryonic stem cells              | Embryonic stem cells can be massively amplified and have pluripotent potentials; these cells can differentiate into all types of cells in vivo. | The application of embryonic stem cells is restricted by incomplete culture methods, transplantation rejection and risk of tumor formation, ethics problem. |
| Umbilical cord blood stem cells   | Umbilical cord blood stem cells have easy and wide sources, low immune rejection, and application potential in clinics | Due to low immunogenicity, low antigen expression and low activities, umbilical cord blood stem cells cannot be massively separated, purified, amplified and stored. |

Table 2 Number of articles published on different types of stem cell transplantation for stroke treatment

| Publication time (year) | Neural stem cells | Bone marrow mesenchymal stem cells | Embryonic stem cells | Umbilical cord blood stem cells |
|-------------------------|-------------------|-----------------------------------|----------------------|--------------------------------|
| 2004                    | 53                | 6                                 | 11                   | 6                              |
| 2005                    | 47                | 16                                | 17                   | 7                              |
| 2006                    | 72                | 21                                | 23                   | 12                             |
| 2007                    | 94                | 20                                | 25                   | 10                             |
| 2008                    | 96                | 41                                | 29                   | 14                             |
| 2009                    | 141               | 60                                | 44                   | 19                             |
| 2010                    | 124               | 78                                | 32                   | 26                             |
| 2011                    | 141               | 62                                | 25                   | 26                             |
| 2012                    | 141               | 91                                | 28                   | 25                             |
| 2013                    | 183               | 122                               | 31                   | 24                             |

Table 3 Highly cited articles on stem cell transplantation for stroke treatment

| Title                                                                 | First author | Journal                              | Publication time (year) | Total citation frequency | Average citation frequency |
|-----------------------------------------------------------------------|--------------|--------------------------------------|-------------------------|--------------------------|---------------------------|
| Transplanted human fetal neural stem cells survive, migrate, and differentiate in ischemic rat cerebral cortex | Kelly S      | Proceedings of the National Academy of Sciences of the USA | 2004                     | 293                       | 26.64                      |
| The science of stroke: mechanisms in search of treatments             | Moskowitz MA | Neuron                               | 2010                    | 287                       | 57.40                      |
| Central nervous system entry of peripherally injected umbilical cord blood cells is not required for neuroprotection in stroke | Borlongan CV | Stroke                               | 2004                    | 230                       | 20.91                      |
| Activated neural stem cells contribute to stroke-induced neurogenesis and neuroblast migration toward the infarct boundary in adult rats | Zhang RL     | Journal of Cerebral Blood            | 2004                    | 212                       | 19.27                      |
| Functional recovery of stroke rats induced by granulocyte colony-stimulating factor-stimulated stem cells | Shyu WC      | Circulation                          | 2004                    | 203                       | 18.45                      |
| SDF-1 (CXCL12) is upregulated in the ischemic penumbra following stroke: Association with bone marrow cell homing to injury | Hill WD      | Journal of Neuropathology and Experimental Neurology | 2004                    | 194                       | 17.64                      |
| Mesenchymal stem cells that produce neurotrophic factors reduce ischemic damage in the rat middle cerebral artery occlusion model | Kurozumi K | Molecular Therapy                     | 2005                    | 193                       | 19.30                      |
The majority of published articles were financially supported by NIH (143 articles, 6.6%), the National Natural Science Foundation of China (91 articles, 4.2%), and other agencies (< 50 articles).

NIH-funded ongoing projects on stem cell transplantation for stroke treatment

NIH not only conducts scientific research engaged in medical fields, but also provides major biomedical research funding to non-NIH research facilities, such as universities, medical colleges, hospitals, and other research institutions. In addition, NIH assists in staff training and promotes exchange of medical information.

During 2013–2014, NIH provided financial support for 329 ongoing research projects on stem cell transplantation in stroke treatment (Table 7), with total funding of over $130 million. In 2014, 215 projects were newly approved, with funding of $70,444,022 and an average project fund of $328,000. Of the 329 NIH-funded research projects, 141 articles were financially supported by the National Institute of Neurological Disorders and Stroke, with up to $58,700,000 of subsidy and an average project fund of $416,000. The NIH Heart, Lung, and Blood Institute was second, with total funds of up to $15,020,000.

Analysis of the Clinical Trial Registration Program in North America

The North American Clinical Trial Data Center (http://www.

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Table 4 Types of published articles on stem cell transplantation for stroke treatment

| Type                    | Number of publications | Percentage (%) |
|-------------------------|------------------------|----------------|
| Article                 | 1,535                  | 70.8           |
| Review                  | 395                    | 18.2           |
| Meeting abstract        | 147                    | 6.8            |
| Proceedings paper       | 79                     | 3.7            |
| Editorial material      | 46                     | 2.1            |
| News item               | 13                     | 0.6            |

Meeting abstracts may also be included as original research, therefore the total number of all types of articles is higher than the number of included articles.

Table 5 Top ten journals publishing articles on stem cell transplantation for stroke treatment

| Journal                              | Number of publications | Percentage (%) |
|--------------------------------------|------------------------|----------------|
| Stroke                               | 145                    | 6.7            |
| Brain Research                       | 72                     | 3.3            |
| Cell Transplantation                 | 70                     | 3.2            |
| Journal of Cerebral Blood Flow and Metabolism | 63                     | 2.9            |
| PLOS ONE                             | 57                     | 2.6            |
| Experimental Neurology               | 51                     | 2.4            |
| Journal of Neuroscience Research     | 41                     | 1.9            |
| Neuroscience                         | 34                     | 1.6            |
| Neuroscience Letters                 | 33                     | 1.5            |
| Neural Regeneration Research         | 28                     | 1.3            |

Table 6 Funding agencies responsible for published articles on stem cell transplantation for stroke treatment

| Funding agency                        | Number of publications | Percentage (%) |
|---------------------------------------|------------------------|----------------|
| National Institutes of Health         | 143                    | 6.6            |
| National Natural Science Foundation of China | 91                     | 4.2            |
| European Union                        | 39                     | 1.8            |
| Swedish Research Council              | 24                     | 1.1            |
| NIH NINDS                             | 23                     | 1.1            |

The majority of published articles were financially supported by NIH (143 articles, 6.6%), the National Natural Science Foundation of China (91 articles, 4.2%), and other agencies (< 50 articles).

NIH-funded ongoing projects on stem cell transplantation for stroke treatment

The North American Clinical Trial Data Center (http://www.

Table 7 Number of ongoing NIH projects and funding for stem cell transplantation in stroke treatment

| Fiscal year | Projects | Project funding | % of total funding |
|-------------|----------|-----------------|--------------------|
| 2010        | 2        | $3,480,000      | 2.6                |
| 2011        | 5        | $2,745,327      | 2.1                |
| 2012        | 19       | $9,992,988      | 7.6                |
| 2013        | 88       | $45,614,937     | 34.5               |
| 2014        | 215      | $70,444,022     | 53.3               |
| Total       | 329      | 132,277,274     | 100                |

Table 8 Regions of registered clinical trials on stem cell transplantation for stroke treatment in the North American Clinical Trial Data Center

| Region            | Number of Studies |
|-------------------|-------------------|
| North America     | 43                |
| Europe            | 25                |
| East Asia         | 11                |
| Middle East       | 1                 |
| South America     | 2                 |
| South Asia        | 5                 |
| Southeast Asia    | 3                 |
| World             | 90                |
clinicaltrials.gov/) was jointly developed by the NIH, National Library of Medicine (NLM), and United States Food and Drug Administration (FDA) in February 2000. The aim of the North American Clinical Trial Data Center is to report in a timely manner, clinical trial information sponsored by NIH, other federal government agencies, and private enterprises, and receives > 50 million page views per month and > 65,000 visitors per day. Of all registered clinical trials, 52,381 projects were from the USA (accounting for 51%), while over 7,000 clinical trials were registered by Chinese researchers. Registration areas for clinical trials on stem cell transplantation for stroke treatment are shown (Table 8).

Ninety clinical trials are registered in the North American Clinical Trial Data Center. Of these, 40 projects are registered in North America (ranked first place), followed by Europe, with the UK responsible for seven projects, France six, Germany six, and Spain four. In Asia, China has the most ongoing research projects or completed clinical trials (n = 10).

Discussion

In the past 10 years, an increasing amount of literature has highlighted the use of stem cell transplantation for stroke treatment. In 2008, only 87 articles were published, increasing to 388 in 2013. Different stem cell types have been widely applied for stroke treatment, with a sharp increase in the number of studies addressing neural stem cell transplantation, followed by bone marrow mesenchymal stem cell transplantation. Embryonic and umbilical cord blood stem cell transplantation are rarely documented, showing no significant increase in number of related studies.

We found that from 2004–2013, the USA is the most SCI-indexed country for articles on stem cell transplantation for stroke treatment, publishing the most literature and highlighting the contribution of this country to medical research in the stroke field. China ranks second, publishing 292 articles. The top publication institutions for articles are Oakland University, Henry Ford Hospital, and University of Florida, all located in the USA. Knowledge of key institutions for stem cell transplantation will facilitate technical exchange and research cooperation among experts.

Of the funding agencies responsible for supporting projects on stem cell transplantation for stroke treatment, NIH provides financial support for 143 articles (accounting for 6.6% of total literature), while the National Natural Science Foundation of China funded 91 articles, demonstrating China's contribution to the field of stem cell transplantation.

At present, NIH provides considerable funds for medical research addressing stem cell transplantation for stroke treatment, funding 329 ongoing projects with over $130 million of total subsidy.

Among the 90 clinical trials registered in the North America Clinical Trial Data Center, 40 projects were registered in North America (occupying first place), followed by Europe with UK (7 projects), France (6 projects), Germany (6 projects), and Spain (4 projects). In Asia, China has the maximum ongoing research or completed clinical trials (10 projects).

In recent years, stem cell transplantation has become a hot spot for stroke treatment, but its clinical application has been greatly restricted (Buchan et al., 2001; Pollock et al., 2006). Further work is needed to determine a stem cell source, transplantation approach, safety of cell transplantation, therapeutic time window, therapeutic dose, route of administration, choice of cell lines, indications, long-term effects and risk assessment, stem cell survival and integration in the host (Nelson et al., 2002; Chu et al., 2004). Currently, there is no strong evidence showing that transplanted stem cells can replace damaged cells, reconstruct neural circuits, or improve loss of function after stroke (Fan et al., 2010; Darsalia et al., 2011), and many questions remain. For example, how can neurological recovery in transplant recipients be promoted, and how can tumorigenicity, pathogenicity, and immune rejection of transplanted stem cells be detected? (Bühnemann et al., 2006; Hacke et al., 2008). Resolution of these problems will allow broader application of neural stem cell transplantation.

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