



## Bibliometric and Visualized Analysis of Stem Cells Therapy for Spinal Cord Injury Based on Web of Science and CiteSpace in the Last 20 Years

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■ **OBJECTIVE:** To provide an analysis of Web of Science (WoS) indexed literature related to stem cells therapy in spinal cord injury published between 1999 and 2018.

■ **METHODS:** Data were obtained from the WoS Core Collection on March 30, 2019. Qualitative and quantitative analysis was conducted based on WoS. Co-citation analysis, collaboration analysis, and co-words analysis of keywords was conducted by using CiteSpace.

■ **RESULTS:** A total of 4188 references were obtained. The number of publications continually increased over the investigated period. Articles were the most frequently document type. *Cell Transplantation* (127) was the most productive journal. *Experimental Neurology* (2180) was the most frequently co-cited journal. H. Okano was the most productive and influential author, with 98 publications and 4860 cited counts. The most productive country and institution were the United States and University of Toronto, respectively. Researchers and institutions from Canada, the United States, Japan, and China were the core research forces. There was a broad and close cooperation worldwide. The Lu et al.'s (2012) article (co-citation counts, 177) was the most representative and symbolic reference. Transplantation, functional recovery, marrow-derived mesenchymal stem cell treatment, and progenitor cells were the hot spots. Inflammation, glial scar, nerve regeneration, neurite outgrowth, and bone marrow stromal cell were research frontiers.

■ **CONCLUSIONS:** Research on stem cells for spinal cord injury is a well-developed and promising research field. There is broad global scientific research cooperation. More cooperation among top authors, institutions, and countries is needed. Our results may be helpful for researchers in identifying further potential perspectives on collaborators, research frontiers, and hot topics.

### INTRODUCTION

Spinal cord injury (SCI) is a severe and disabling disease. Because of car accidents, the construction industry, and so on, patients with SCI are an increasing trend. The annual incidence of SCI worldwide varies from 8 to 246 per million persons per year.<sup>1,2</sup> Despite considerable progress in early treatment and understanding of the pathogenesis, SCI remains a devastating event, often causing severe and permanent disability. The treatment and rehabilitation of SCI remain costly issue for families and society. Stem cell therapy may be a revolutionary treatment for repairing damaged spinal cords.<sup>3,4</sup> This new direction has attracted many researchers, and much literature has emerged in this area.

Bibliometrics is a series of analyses for evaluating or quantifying literature and information. The Web of Science (WoS) Core Collection is the most frequently used citation database for bibliometric analysis.<sup>5</sup> The WoS can provide the following information: annual output, authors, journals, institutions,

#### Key words

- Bibliometric analysis
- CiteSpace
- Co-citation
- Co-occurrence
- Spinal cord injury
- Stem cells

#### Abbreviations and Acronyms

- IF: Impact factor
- iPSC: Induced pluripotent stem cells
- NIH: National Institutes of Health
- SCI: Spinal cord injury
- WoS: Web of Science

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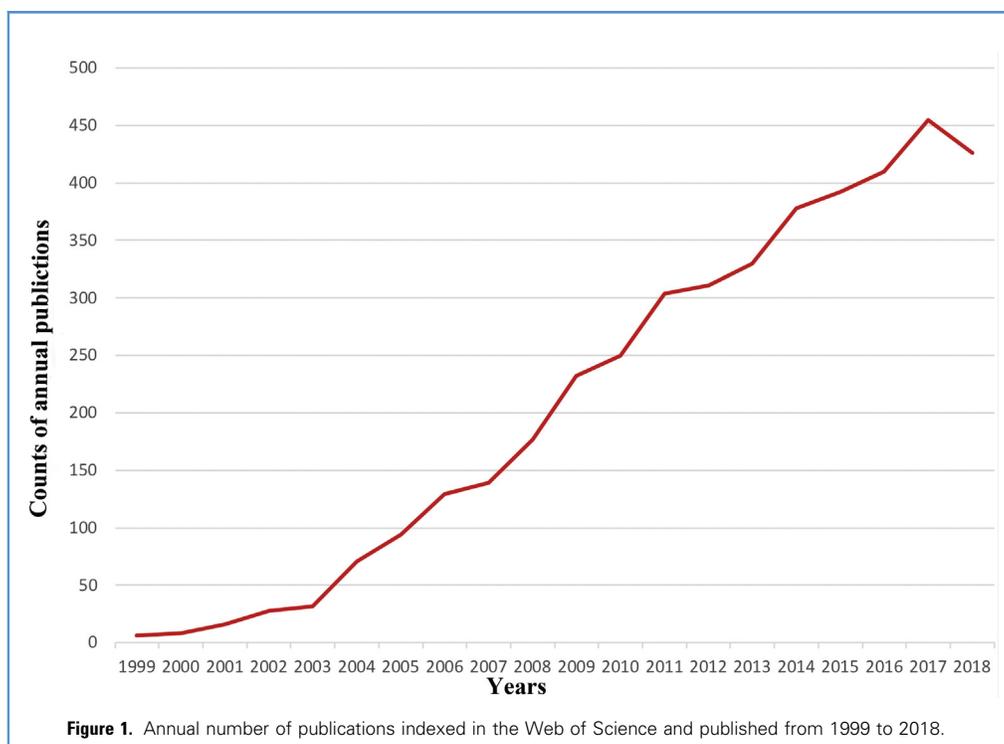
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countries/territories, languages, and funds. CiteSpace has become a popular tool for bibliometric analysis in recent years and was developed by Chen.<sup>6</sup> It can identify the core researchers, institutions, and countries in a special field and the cooperative relationship between them. Co-words analysis of keywords or terms can reflect the global research trends and topic hotspots. In addition, co-citation analysis can identify the research foundation in the field. Moreover, it can generate visual knowledge maps. A

bibliometric analysis of stem cell treatment for SCI was reported in 2012.<sup>7</sup> In that study, stem cell types were limited to neural stem cells, Schwann cells, and olfactory ensheathing cells. The number of publications was only a few hundred. Several kinds of stem cell types, including bone marrow mesenchymal stem cells and induced pluripotent stem cells (iPSC), were researched for treating SCI. Many studies have emerged since 2012, and global research has changed. It is necessary and meaningful to conduct further bibliometric analysis of this literature. Therefore, aiming to identify core journals, research trends, and frontiers in this field, along with core researchers, institutions, and countries as well as their collaboration, we performed a bibliometric analysis and created visual knowledge maps of the literature on stem cells for SCI over the past 20 years based on WoS and CiteSpace.

Ranking	Funding Source	Frequency
1	National Natural Science Foundation of China	322
2	National Institutes of Health	263
3	National Institute of Neurological Disorders and Stroke National Institutes of Health U.S. Department of Health and Human Services	123
4	Medical Research Council	61
5	Craig H Neilsen Foundation	54
6	Canadian Institutes of Health Research	36
7	Natural Science Foundation of China	30
8	General Insurance Association of Japan	27
9	National Science Foundation	25
10	Swedish Research Council	24

## METHODS

A search for articles related to stem cells for SCI was conducted in the WoS Core Collection (SCI-EXPANDED, CPCI-S, CCR-EXPANDED, and IC) on March 30, 2019. The search formula was (TS=["spinal injur\*" OR "spinal cord injur\*" OR "spinal cord traum\*" OR "spinal traum\*" OR paraplegia OR quadriplegia OR tetraplegia]) AND (TS=["stem cell" OR "stem cells"]). The search period was set from 1999 to 2018, and the document types included articles, reviews, meeting abstracts, and proceedings articles. First, a WoS-based literature analysis was conducted to understand the general information about annual output, authors, journals, institutions, countries/territories, languages, and funds. Then, CiteSpace software (5.3.R4.8) was used to identify the top

**Table 2.** The Top 10 Journals with Most Published Literature from 1999 to 2018

Ranking	Journal	Publications	Times Cited	Times Cited (per Article)	Impact Factor
1	<i>Cell Transplantation</i>	127	3205	25.2	2.89
2	<i>Journal of Neurotrauma</i>	116	2917	25.2	5.00
3	<i>Neural Regeneration Research</i>	114	535	4.7	2.23
4	<i>Experimental Neurology</i>	93	5190	55.8	4.48
5	<i>PLoS One</i>	93	2621	28.2	2.77
6	<i>Biomaterials</i>	71	3772	53.1	8.81
7	<i>Stem Cells</i>	62	4148	66.9	5.59
8	<i>Brain Research</i>	56	1857	33.2	3.13
9	<i>Journal of Neuroscience Research</i>	56	3221	57.5	2.66
10	<i>Cytotherapy</i>	55	1455	26.5	3.99

authors, institutions, countries, and research cooperation relationships (co-occurrence analysis of author, institution, and country). Third, we performed co-citation network analysis of reference, author, and journal to clarify the research base in this field. Cutting-edge knowledge and research trends were obtained through co-word network analysis of keywords.

The parameters of CiteSpace were set as follows: time slicing (1999–2018), years per slice (1), term source (all selection), node type (choose 1 at a time), selection criteria (top 50 objects), and pruning (pathfinder). For each node type, we analyzed the node size (the size of a node, which meant the frequency of occurrence or citation), betweenness centrality (if  $\geq 0.1$ , then marked with a purple ring, which meant a key node in the collaboration or co-citation network), explosiveness (a red ring), and spotlight of important nodes. The link line between 2 nodes means that there was a cooperative relationship (between authors, institutions, or countries/territories) or a co-citation relationship (for reference, authors, or journals) between those 2 nodes. Cluster network

analysis of co-cited reference, co-cited authors, and co-words of keywords was conducted. The Q value of the cluster network represented the modularity of the network. The larger the Q value, the better the cluster of the network. When  $Q > 0.3$ , the network cluster structure was significant.<sup>8</sup> The silhouette value is an indicator used to measure the homogeneity of the cluster network. The closer the silhouette value was to 1, the higher the homogeneity of the cluster network. When the silhouette value was  $> 0.7$ , the clustering result had high reliability.<sup>8</sup>

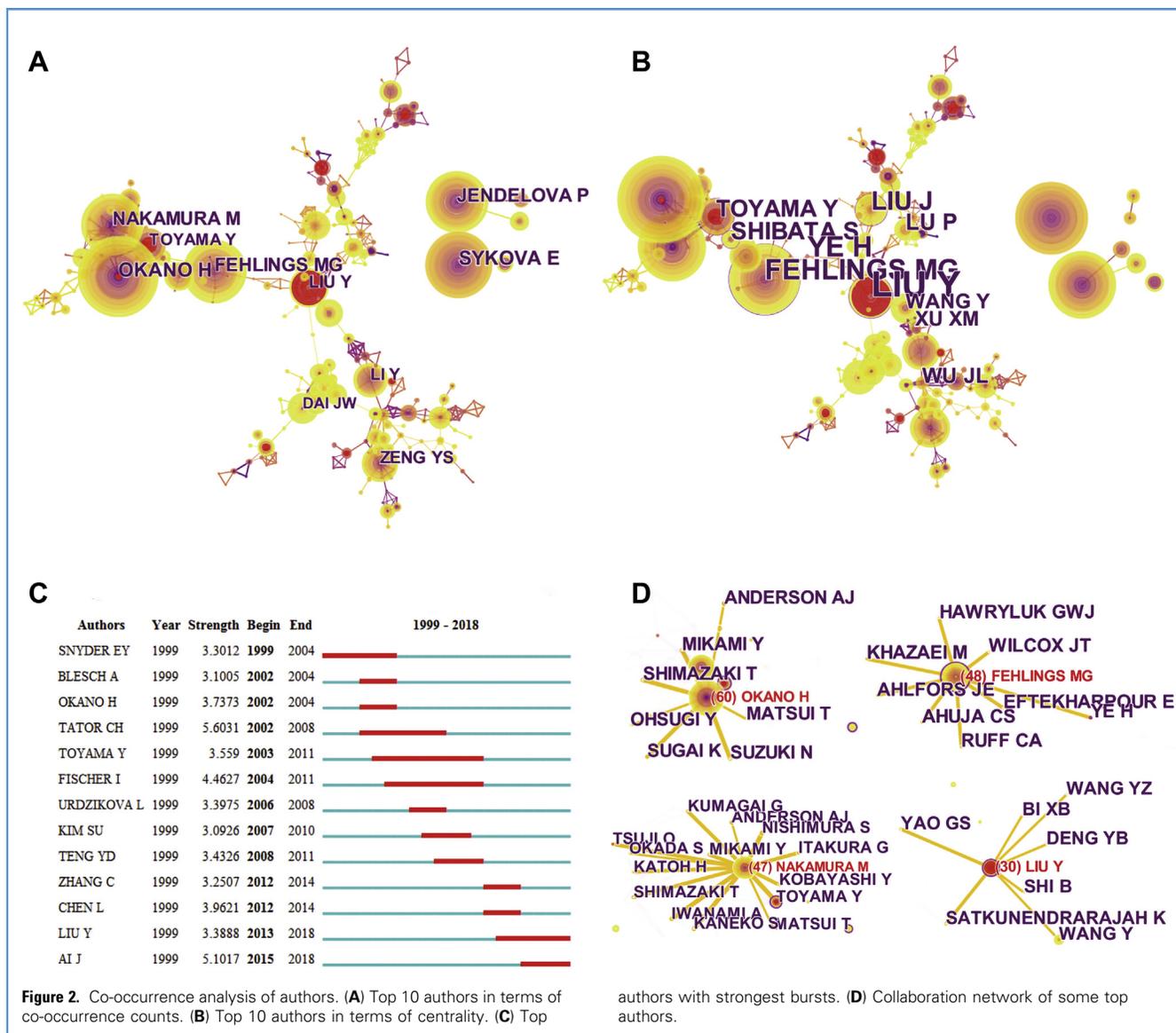
## RESULTS

### Publication Outputs

There were 343,555 and 49,011 items on stem cells and SCI, respectively, on the WoS Core Collection. When conducting the logical algorithm of “AND,” there were 4188 articles, mainly including 3053 articles, 952 reviews, 157 meeting abstracts, and 99 proceedings articles. More than 99% (4145/4188) of the literature

**Table 3.** The Top 10 Active Authors with Most Publications from 1999 to 2018

Ranking	Author	Publications	Institution	Times Cited	Times Cited (per Article)
1	H. Okano	98	Keio University	4860	49.6
2	M. Nakamura	75	Keio University	3555	47.4
3	E. Sykova	73	Czech Academy of Sciences	2118	29.0
4	P. Jendelova	61	Charles University	1661	27.2
5	M.G. Fehlings	58	University of Toronto	3262	56.2
6	Y. Toyama	53	Keio University	3010	56.8
7	Y. Liu	47	Krembil Research Institute	1030	21.2
8	Y. Li	45	Sun Yat Sen University	1351	30.0
9	Y.S. Zeng	42	Sun Yat Sen University	1018	24.2
10	I. Fischer	37	Drexel University	2217	59.9



**Figure 2.** Co-occurrence analysis of authors. (A) Top 10 authors in terms of co-occurrence counts. (B) Top 10 authors in terms of centrality. (C) Top

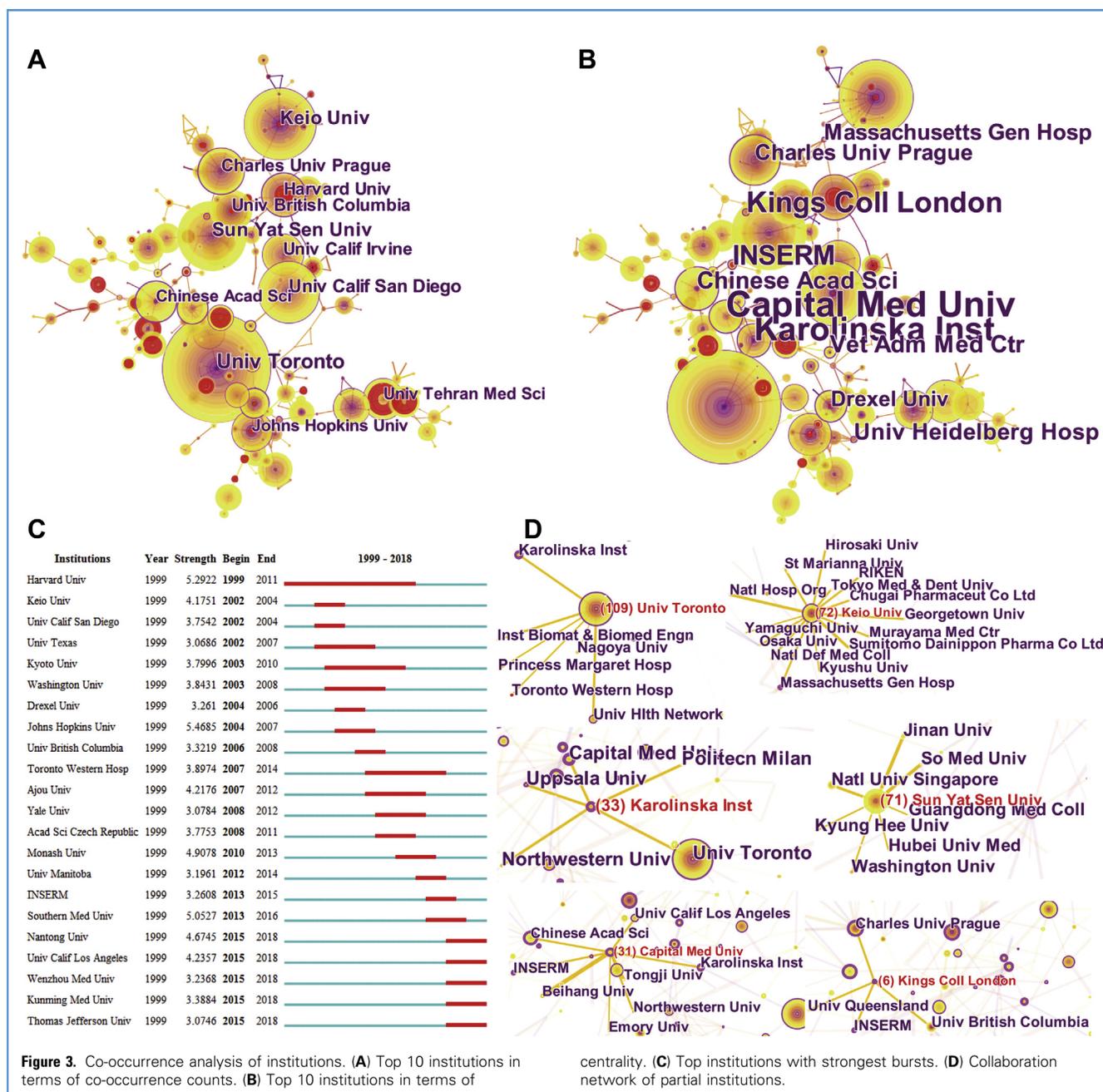
authors with strongest bursts. (D) Collaboration network of some top authors.

was published in English. **Figure 1** shows the counts of annual publication. The studied period could be divided into 2 stages: the first from 1999 to 2003 and the second from 2004 to 2018. The rate of growth was relatively slow in the first stage. In the second stage, the publication number showed a steady increasing trend averaging about 30 articles annually, except in 2018. In 1999, there were only 6 articles, and this number exceeded 100, 200, 300, and 400 in 2006, 2009, 2011, and 2016, respectively. In 2017, it reached a peak of 455 articles and decreased slightly to 426 in 2018. In total, 4483 sources of funding have supported some research in this area. The top 10 major sources of funding are shown in **Table 1**, and the National Natural Science Foundation of China, U.S. National Institutes of Health (NIH), NIH National Institute of Neurological Disorders and Stroke of the U.S. Department of

Health and Human Services were the top 3 funding sources. In 1999, there were only 6 articles, and this number exceeded 100, 200, 300, and 400 in 2006, 2009, 2011, and 2016, respectively. In 2017, a peak of 455 articles was reached, with a slight decrease to 426 in 2018. A total of 4483 sources of funding have supported some research in this area. The top 10 major funds are shown in **Table 1**, and the National Natural Science Foundation of China, NIH, and National Institute of Neurological Disorders and Stroke were the top 3 funding sources.

**Journals Analysis**

In total, 946 journals published research literature related to stem cells for SCI from 1999 to 2018. **Table 2** presents the top 10 journals that published the most articles. These 10 journals published about 20.0% of the literature. Cell Transplantation was



the most active journal in this field, followed by *Journal of Neurotrauma* and *Neural Regeneration Research*. All 10 journals had an impact factor (IF) >2.00, and *Biomaterials* had the maximum IF of 8.80. The articles published in some journals were cited >50 times on average, such as *Stem Cells*, *Journal of Neuroscience Research*, *Experimental Neurology*, and *Biomaterials*. These are professional and active journals in this special field. In addition, a few articles were published in journals with a high IF, such as *Science* (IF, 41.05) and *Cell* (IF, 31.40).<sup>9,10</sup>

### Scientific Collaboration Network Analysis

The 4188 articles on stem cells for SCI were drafted by about 14,528 authors. **Table 3** shows the top 10 authors with the largest number of publications and their institutions. They were professional and active authors in this field. A co-occurrence map of authors was generated by CiteSpace. **Figure 2A** shows the maximum subnetwork of the co-authorship. The top 3 ranked by co-occurrence counts were H. Okano (64), E. Sykova (50), and M.G. Fehlings (48). The top 3 authors by centrality were

**Table 4.** The Top 10 Institutions in Terms of Publications, Co-Publish Counts, and Centrality

Ranking	Publications	Institution	Co-Publish Counts	Institution	Centrality	Institution
1	125	University of Toronto	109	University of Toronto	0.34	Capital Medical University
2	111	Keio University	72	Keio University	0.32	Karolinska Institutet
3	94	Sun Yat Sen University	71	Sun Yat Sen University	0.28	Kings College London
4	75	University of California San Diego	62	University of California San Diego	0.26	INSERM
5	68	Harvard University	48	Charles University Prague	0.23	Chinese Academy of Sciences
6	62	Charles University Prague	44	University of British Columbia	0.23	Veterans Administration Medical Center
7	62	University of British Columbia	43	Harvard University	0.22	University Hospital of Heidelberg
8	59	University of California Irvine	42	University of California Irvine	0.22	Massachusetts General Hospital
9	59	Yonsei University	41	University of Tehran Medical Science, Johns Hopkins University, Chinese Academy of Sciences	0.21	Charles University Prague
10	56	Johns Hopkins University			0.21	Drexel University

Y. Liu, M.G. Fehlings, and H. Ye (Figure 2B). Authors who had published the most articles had extensive relationships with others (Figure 2D). H. Okano had a lot of cooperation with these authors: Y. Ohsugi, T. Shimazaki, Y. Mikami, A.J. Anderson, K. Sugai and N. Suzuki. Authors who worked closely with M. Nakamura included Y. Toyama, S. Nishimura, T. Shimazaki, Y. Mikami, and S. Kaneko. The top 2 authors, H. Okano and M. Nakamura, were both from Keio University (Japan), and they had strong collaborations. They studied human iPSCs.<sup>11-13</sup> They reported a clinical research protocol, aiming at observing and solving the safety, tumorigenesis, and practical problems of iPSC-based cell transplant intervention for subacute SCI.<sup>11</sup> In addition, Figure 2C shows the authors with the strongest bursts. The number of articles they published increased rapidly in this area during a certain period. The top 3 ranked authors by burst were C.H. Tator, J. Ai, and I. Fischer.

A total of 3203 research institutions had articles published in the past 2 decades. The maximum subnetwork of cooperation between institutions is shown in Figure 3. Table 4 shows the top 10 institutions in terms of publications, co-occurrence counts, and centrality. The top 3 ranked items by co-occurrence counts were University of Toronto, Keio University, and Sun Yat Sen University. The top 3 institutions by centrality were Capital Med University, Karolinska Institutet, and Kings College London. The top 4 institutions that published the most articles were as the same as the top 4 that cooperated most frequently with other institutions. For burst monitoring, there were 22 institutions (Figure 3C). The top 3 ranked items were Johns Hopkins University, burst from 2004 to 2007, followed by Harvard University burst from 1999 to 2011, and Southern Medical University burst from 2013 to 2016.

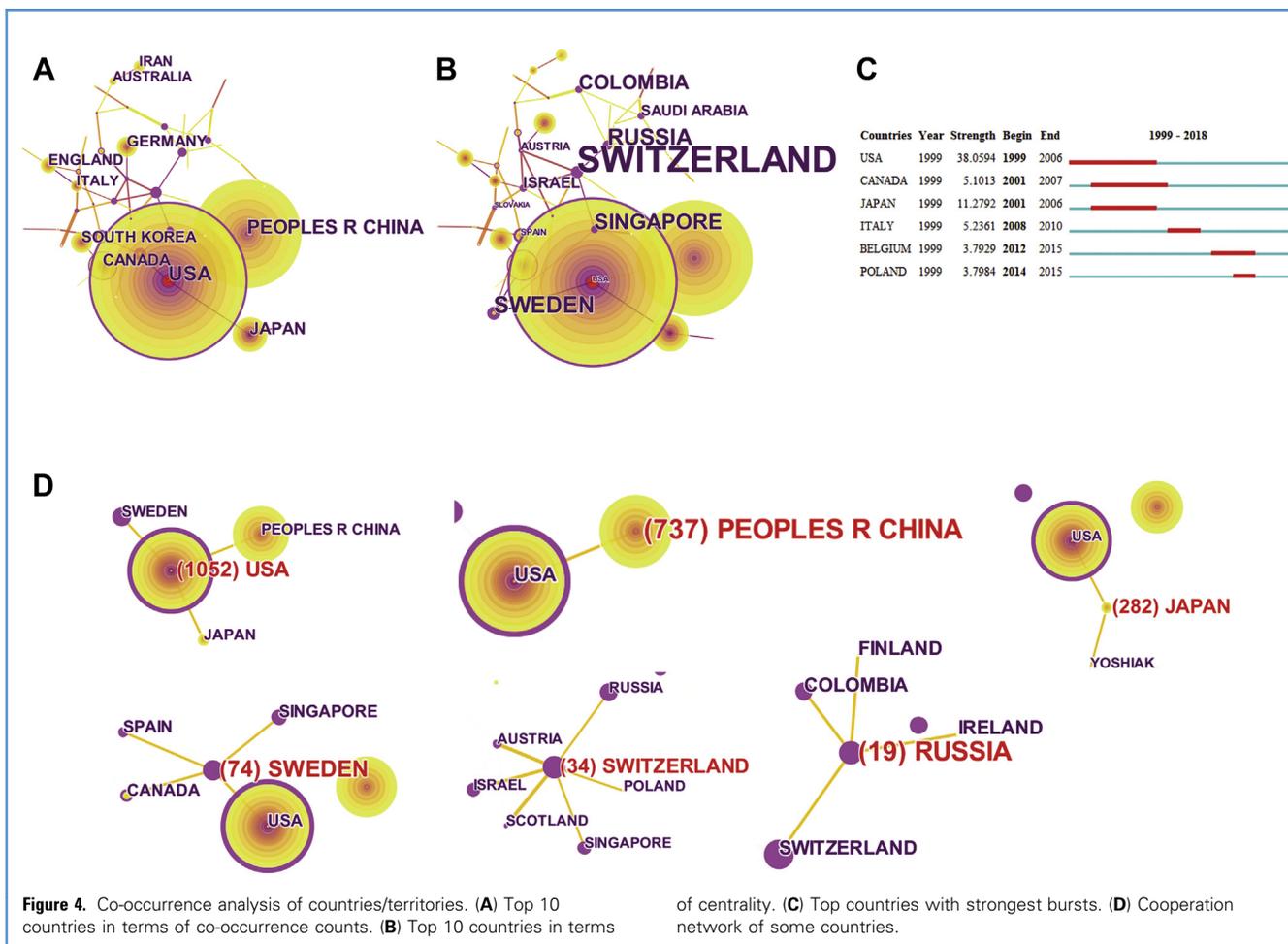
Each top organization had extensive relationships with other agencies (Figure 3D). For example, the important research partners of University of Toronto included Karolinska Institutet, University Health Network, Toronto Western Hospital, Institute of Biomaterials and Biomedical Engineering, Nagoya University, and Princess Margaret Hospital. Keio University had extensive

cooperation with >10 organizations, such as National Hospital Oregon, Hiroasaki University, Massachusetts General Hospital, Georgetown University, Osaka University, and Tokyo Medical and Dental University. Although Capital Medical University did not have so many published articles, it had cooperated with many institutions, such as the Chinese Academy of Science, Beihang University, Northwestern University, University of California Los Angeles, Tongji University, and Karolinska Institutet. Top institutions had relatively limited cooperation with each other.

Articles on this topic were published by 70 countries/territories. The collaboration network map is presented in Figure 4. The top 10 countries in terms of publications, collaboration counts, and centrality are listed in Table 5. The top 3 ranked countries/territories by co-occurrence counts were the United States, China, and Japan (Figure 4A). The top 3 countries by centrality were Switzerland, Sweden, and Russia (Figure 4B). There was a certain degree of cooperation between countries (Figure 4D). The important research cooperators of the United States were Japan, Sweden, and China. China had close cooperation with the United States. Switzerland had a partnership with many countries, such as Austria, Israel, Singapore, Russia, Scotland, and Poland. In addition, the countries with the strongest bursts in the amount of publications are shown in Figure 4C. The analysis of publications and centrality suggested that the United States, China, and Japan were the main research forces in this field.

### Co-citation Analysis

The concept of co-citation is used as a research method to measure the degree of relationship between documents. More than 106,197 references were cited by the 4188 articles. The top 10 references with the most co-citation counts are presented in Table 6.<sup>10,14-22</sup> A total of 63 clusters with an overall  $Q = 0.8681$  comprised the cluster map; the maximum subnetwork of the co-citation map and cluster map are shown in Figure 5A and B.



**Table 5.** The Top 10 Countries/Territories in Terms of Publications, Co-Occurrence Counts, and Centrality

Ranking	Publications	Countries/Territories	Counts of Co-Occurrence	Countries/Territories	Centrality	Countries/Territories
1	1373	United States	1052	United States	0.95	Switzerland
2	927	Peoples Republic of China	737	Peoples Republic of China	0.62	Sweden
3	402	Japan	282	Japan	0.61	Russia
4	289	Canada	235	Canada	0.57	Singapore
5	251	South Korea	177	South Korea	0.54	Colombia
6	228	Germany	166	Germany	0.42	Israel
7	197	England	150	England	0.4	Saudi Arabia
8	172	Italy	125	Italy	0.31	Austria
9	131	Spain	108	Iran	0.24	Spain
10	132	Iran	91	Australia	0.21	United States

**Table 6.** The Top 10 References with Most Co-Citation Counts

Ranking	Co-Citation Counts	Cited Reference	Representative Author (Publication Year)	Journal	Impact Factor
1	177	Long-distance growth and connectivity of neural stem cells after severe spinal cord injury <sup>10</sup>	P. Lu (2012)	<i>Cell</i>	31.40
2	160	Human embryonic stem cell-derived oligodendrocyte progenitor cell transplants remyelinate and restore locomotion after spinal cord injury <sup>14</sup>	H.S. Keirstead (2005)	<i>Journal of Neuroscience</i>	5.98
3	128	A systematic review of cellular transplantation therapies for spinal cord injury <sup>15</sup>	W. Tetzlaff (2011)	<i>Journal of Neurotrauma</i>	5.00
4	124	Therapeutic potential of appropriately evaluated safe-induced pluripotent stem cells for spinal cord injury <sup>16</sup>	O. Tsuji (2010)	<i>Proceedings of the National Academy of Sciences of the U S A</i>	9.50
5	121	Delayed transplantation of adult neural precursor cells promotes remyelination and functional neurological recovery after spinal cord injury <sup>17</sup>	S. Karimi-Abdolrezaee (2006)	<i>Journal of Neuroscience</i>	5.97
6	116	Grafted human-induced pluripotent stem-cell-derived neurospheres promote motor functional recovery after spinal cord injury in mice <sup>18</sup>	S. Nori (2011)	<i>Proceedings of the National Academy of Sciences of the U S A</i>	9.50
7	113	Neural stem cells constitutively secrete neurotrophic factors and promote extensive host axonal growth after spinal cord injury <sup>19</sup>	P. Lu (2003)	<i>Experimental Neurology</i>	4.48
8	107	Allodynia limits the usefulness of intraspinal neural stem cell grafts; directed differentiation improves outcome <sup>20</sup>	C.P. Hofstetter (2005)	<i>Nature Neuroscience</i>	19.91
9	106	Human neural stem cells differentiate and promote locomotor recovery in spinal cord-injured mice <sup>21</sup>	B.J. Cummings (2005)	<i>Proceedings of the National Academy of Sciences of the U S A</i>	9.50
10	105	Transplanted embryonic stem cells survive, differentiate, and promote recovery in injured rat spinal cord <sup>22</sup>	J.W. McDonald (1999)	<i>Nature Medicine</i>	32.62

**Table 7** shows the top 10 clusters of the largest subnetwork. An analysis of cluster labels showed that the research foundation over the past 20 years was therapeutic intervention, biomaterial-supported cell transplantation, neural stem cell transplantation, SCI, cellular transplantation therapy, motor function, bridging area, neural transplantation, and the Clarke nucleus neuron.

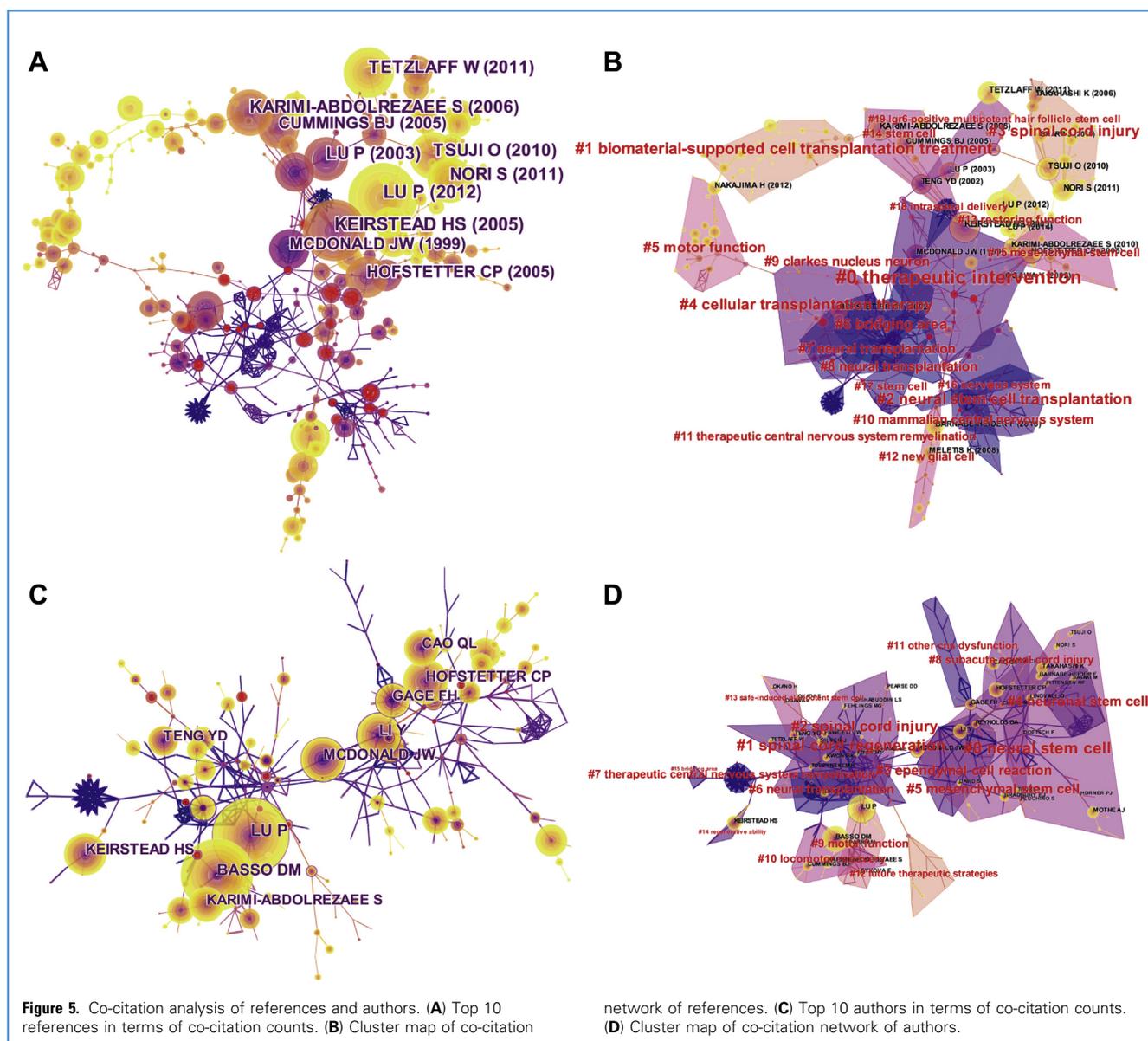
The maximum subnetwork of the co-cited authors and its cluster map are presented in **Figure 5C** and **D**. The top 3 authors by co-citation counts were P. Lu (598 counts), D.M. Basso (561 counts), and C.P. Hofstetter (364 counts). The top 3 authors in terms of centrality were X.M. Xu, B.A. Reynolds, and N.I. Bamber. The top 3 authors with the strongest bursts in the number of co-citation counts included E.Y. Snyder, A. Bjorklund, and E. Mezey. The work of these authors provided the basis for research in this field.

The network of co-cited journals is shown in **Figure 6**. **Table 8** shows the top 10 co-cited journals in terms of co-citation counts and centrality. The top 3 by co-citation counts were *Experimental Neurology*, *Journal of Neuroscience*, and *Proceedings of the National Academy of Sciences of the U S A*. The top 3 journals in terms of centrality included *Molecular and Cellular Neuroscience*, *European Journal*

*of Neuroscience*, and *Trends in Neuroscience*. The articles published in those top journals reflect the basis of the research field.

#### Co-words Analysis of Keywords

A visual knowledge map of keyword co-occurrence could reflect hot and frontier topics. **Figure 7** presents the biggest keywords subnetwork and its cluster map. A total of 16 clusters with an overall  $Q = 0.6582$  made up the co-word network of keywords. Ten had a node number  $>10$  and each had a silhouette value  $>0.7$ . The keywords that appeared most often with transplantation were oligodendrocyte precursor, in vivo, Schwann cell, neuroprotection, progenitor cell, adult rat, in vitro differentiation, neuroregeneration, and fibroblast growth factor. Functional recovery often appeared with the following words: repair, locomotor recovery, olfactory ensheathing glia, neurite growth, SCI, ensheathing cell. Transplantation, axon regeneration, glial scar, cell replacement, generation, and subventricular zone offer appeared with neural stem cell. Regenerative medicine, human bone marrow, injury, growth factor, precursor cell, and neuronal differentiation often emerged at the same time as mesenchymal stem cell. The meaningful keywords with the strongest bursts included inflammation, glial scar, nerve



regeneration, neurite outgrowth, bone marrow stromal cell, embryonic stem cell, olfactory ensheathing glia, and oligodendrocyte (Figure 7C).

## DISCUSSION

We performed a bibliometric and visualized analysis of stem cells for SCI based on WoS and CiteSpace. Our results provide an insight into stem cells for SCI and some valuable information. We found that the number of publications has continually increased over the last 20 years. Cell Transplantation was the most productive journal. *Experimental Neurology* was the most frequently co-cited journal. H. Okano was the most productive and influential author, with 98 publications and 4860 cited counts. The most productive country and institution were the United States and

University of Toronto, respectively. Researchers and institutions from Canada, the United States, Japan, and China were the core research forces and there was a broad and close cooperation in this field worldwide.

## Publication Output

In the last 20 years, the quantity of literature has been increasing year by year. Many researchers have been devoted to this special research field, and more valuable scientific accomplishments have been created. The development track of the past 20 years showed 2 stages: 1999–2003 was the initial period, with a slow development speed, and 2004–2018 was a rapid development period, with a fluctuation in 2018. There were still >400 publications in 2018. This finding means that there may be still some key problems

**Table 7.** Top 10 Clusters of Co-Citation of References

Cluster Number	Cluster Label	Silhouette		
		Size	Value	Mean Year
0	Therapeutic intervention	51	0.853	2003
1	Biomaterial-supported cell transplantation	34	0.951	2011
2	Neural stem cell transplantation	33	0.947	2001
3	Spinal cord injury	33	0.96	2011
4	Cellular transplantation therapy	31	0.913	2004
5	Motor function	29	0.976	2009
6	Bridging area	27	0.856	1998
7	Neural transplantation	26	0.866	1997
8	Neural transplantation	26	0.829	1996
9	Clarke nucleus neuron	26	0.771	2000

waiting to be solved in this field. Therefore, it is still a potential research area, and it is worthwhile investing material resources and labor. This proposal is consistent with the clinical situation. Although there have been much scientific research and some clinical applications in the latest 20 years, stem cell therapy has not yet developed into a conventional treatment or been widely promoted on a large scale. More in-depth research is needed.

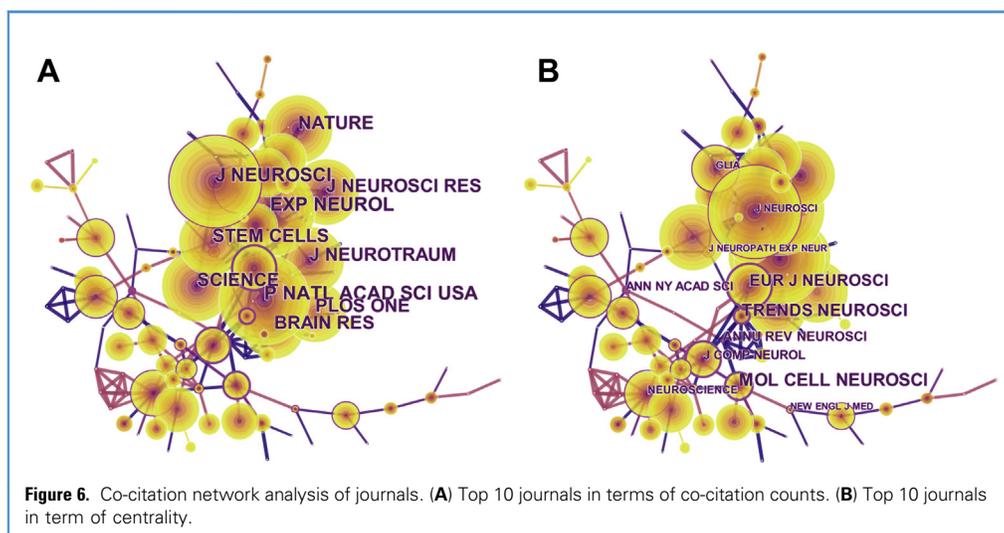
### Journals

The journals analysis could help researchers in choosing appropriate journals for submission of articles. A total of 946 journals published literature in this field. The top 10 journals with the most articles published 20.0%, and the top 20 journals published 30.7% of articles. According to the Bradford law,<sup>23</sup> the top 20 journals are

the core journals in this field. All of the top 10 publication journals had an IF >2.00, and 3 had an IF >5.00. The literature distribution in the journals showed an obvious dispersion. Despite the large number of journals, it seems that no journal had a particularly strong interest in this field, which increases the difficulty for authors in selecting journals. There was a 60% coincidence rate between the top 10 journals in terms of publications and top 10 co-cited journals. Relevant articles in these top co-cited journals formed the key knowledge base in this field. Moreover, 2 journals with a higher IF, *Science* and *Nature*, were ranked fourth and fifth in the co-cited rankings, respectively. This finding means that this field has a reliable research foundation. The most frequently co-cited article in *Nature* was “Chondroitinase ABC promotes functional recovery after spinal cord injury” (E.J. Bradbury, 2002).<sup>24</sup> This article was about chondroitinase ABC on degrading chondroitin sulphate-glycosaminoglycan, inhibiting the glial scar, and promoting regeneration of axons. Stem cells for SCI may be related to this mechanism. The most frequently co-cited literature on *Science* was a review (F.H. Gage, 2000),<sup>25</sup> which focused on the mechanism of controlling neural stem cell proliferation. These findings showed that the research quality and level of stem cells for SCI are reliable.

### Scientific Collaboration Network Analysis

The analyses of distributions in institutions, countries/territories, and authors could help in promoting teamwork and global cooperation in this field. It is also useful for researchers to make the best use of available resources to increase efficiency. The top 10 countries/territories were located in North America (United States and Canada), Asia (China, Japan, and South Korea), and Europe (Germany, the United Kingdom, and Italy). The United States had the largest number of publications. However, among the top 10 authors, only the tenth (I. Fischer) came from Drexel University in the United States. In terms of institutions, Johns Hopkins University and Harvard University were the seventh and ninth, respectively. This situation may be because the researchers and institutions in the United States were scattered. The top 3



**Figure 6.** Co-citation network analysis of journals. (A) Top 10 journals in terms of co-citation counts. (B) Top 10 journals in term of centrality.

**Table 8.** The Top 10 Journals in Terms of Co-Citation Counts and Centrality from 1999 to 2018

Ranking	Co-Citation			Co-Citation			
	Counts	Journal	Impact Factor	Centrality	Journal	Counts	Impact Factor
1	2180	<i>Experimental Neurology</i>	4.48	0.29	<i>Molecular and Cellular Neuroscience</i>	759	3.31
2	2173	<i>Journal of Neuroscience</i>	5.97	0.28	<i>European Journal of Neuroscience</i>	1112	2.83
3	2131	<i>Proceedings of The National Academy of Sciences USA</i>	9.50	0.28	<i>Trends in Neurosciences</i>	461	11.43
4	1742	<i>Science</i>	41.05	0.22	<i>Annual Review of Neuroscience</i>	42	14.77
5	1674	<i>Nature</i>	41.57	0.21	<i>Journal of Comparative Neurology</i>	930	3.40
6	1657	<i>Journal of Neurotrauma</i>	5.00	0.21	<i>Annals of The New York Academy of Sciences</i>	142	4.28
7	1645	<i>Journal of Neuroscience Research</i>	2.66	0.19	<i>Neuroscience</i>	1189	3.38
8	1578	<i>Stem Cells</i>	5.59	0.18	<i>Journal of Neuroscience</i>	2173	5.97
9	1490	<i>Brain Research</i>	2.23	0.17	<i>Glia</i>	1157	5.85
10	1433	<i>PLoS One</i>	4.48	0.17	<i>New England Journal of Medicine</i>	189	79.26

agencies with the highest number of publications were in Canada, Japan, and China. Among the top 10 authors, 3 were from Keio University in Japan, 1 from the Czech Academy of Sciences in the Czech Republic, 1 from Charles University in the Czech Republic, and 2 from Sun Yat Sen University in China. They and their institutions were the main research forces in this area. The institutions and authors from China performed well overall, and this may be related to the large amount of funds invested in this field by the National Natural Science Foundation of China.

The collaboration analysis indicated a broad and close cooperation among researchers all over the world, which shows that the research in this field has a level of maturity. Although some authors, institutions, and countries had a small number of publications, they had a large number of partners. They may be emerging forces in this field and may become the mainstay in the future. However, we discovered that cooperation between top institutions and top authors seems to be insufficient. This situation may be because these top research forces were comparatively fully fledged. They had clear research directions and independent research strength. They were often considered the excellent partners that others sought, and there seems to be no necessity to actively look for more cooperation opportunities.

### Co-citation Analysis

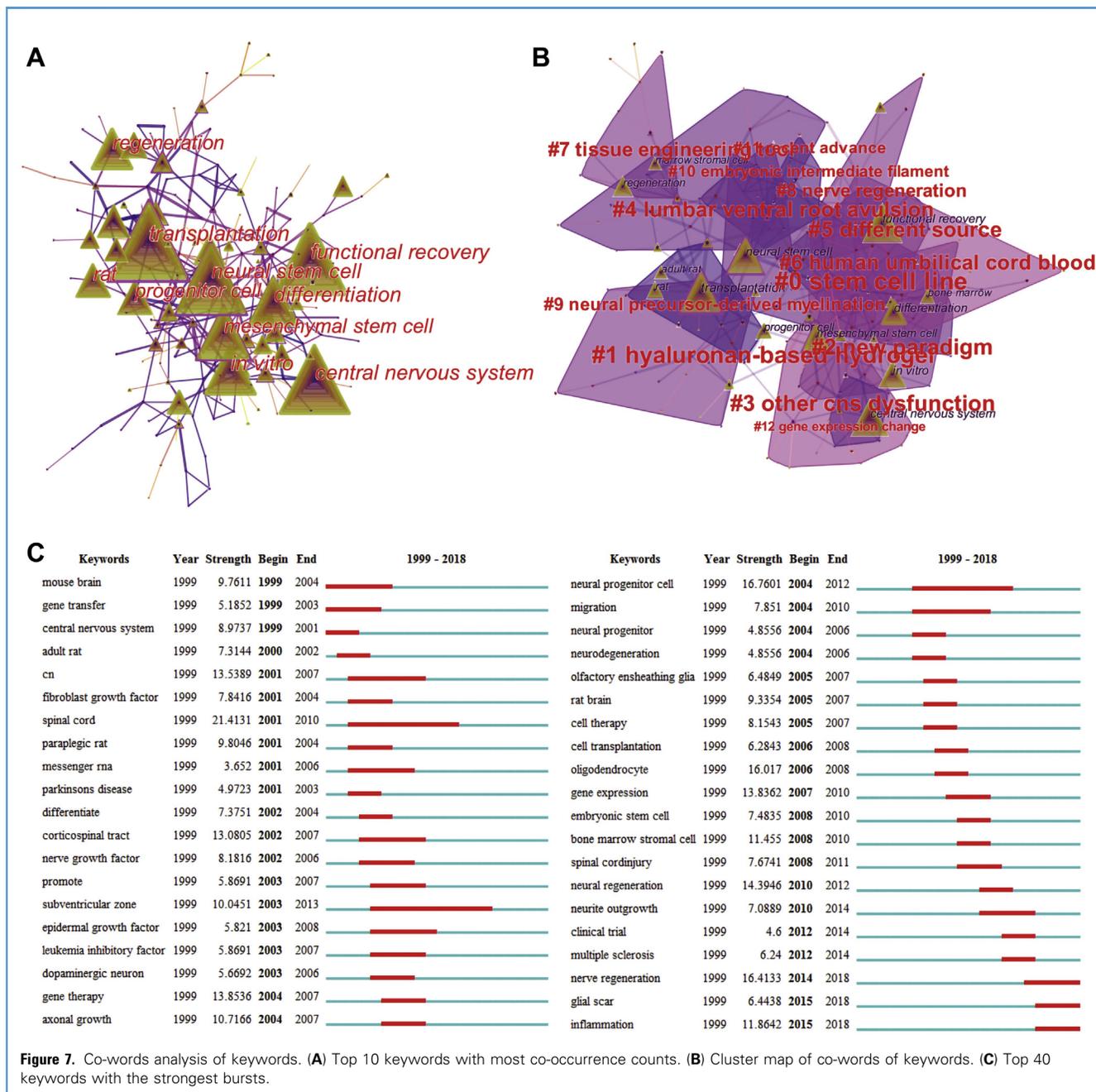
The research articles with the highest co-citation counts comprised the important research foundations in the area. Among them, “Long-distance growth and connectivity of neural stem cells after severe spinal cord injury,” which had the most co-citation times, was the most important foundation.<sup>10</sup> This article reported an extensive number of distance axonal outgrowth from neural stem cell grafts in rats with severe SCI. New synaptic relays and improvement in both electrophysiologic and functional outcome were also observed. The second most co-cited reference was “Human embryonic stem cell-derived oligodendrocyte progenitor cell transplants remyelinate and restore

locomotion after SCI.”<sup>14</sup> This study showed that the transplantation of human embryonic stem cell-derived oligodendrocyte progenitor cells into adult rats with SCI could enhance remyelination and promote the improvement of motor function. These 2 articles investigated the critical points of nerve repair after stem cell transplantation: remyelination and axon growth. Every researcher in the field should be familiar with these important research foundations, which were also helpful in obtaining a first-hand look at key information in the field.

An analysis of co-cited authors showed that P. Lu, D.M. Basso, and C.P. Hofstetter were core strength researchers, and their research had a critical influence on the field. P. Lu was from the Department of Neurosciences, University of California, San Diego. He studied neural stem cells, axonal outgrowth, and connectivity.<sup>26,27</sup> D.M. Basso was based at the Center for Brain and Spinal Cord Repair, Ohio State University, Columbus. He was an expert in SCI. His research was on the measurement model for the neuromuscular recovery after SCI.<sup>28,29</sup> Assessment of motor function is an important way to determine whether the treatment for SCI is effective. Those studies regarding of stem cells for SCI may also involve the assessment of motor function, and this is why D.M. Basso’s research was widely cited.

### Co-Words Analysis of Keywords

According to the co-word analysis of keywords, we found that the most important hot spots in the field over the last 20 years were mesenchymal stem cell, transplantation, functional recovery, and neural stem cell. The frontier topics were inflammation, glial scar, nerve regeneration, neurite outgrowth, bone marrow stromal cell, and embryonic stem cell. Inhibition of inflammation and regulation of glial scars are important mechanisms for stem cell repair in SCI in recent years.<sup>30-32</sup> The keyword “clinical trial” also had a strong burst, suggesting that stem cell therapy for SCI involved translational medicine research. Research in this area was not limited to the laboratory, and the clinical research is gradually



**Figure 7.** Co-words analysis of keywords. (A) Top 10 keywords with most co-occurrence counts. (B) Cluster map of co-words of keywords. (C) Top 40 keywords with the strongest bursts.

increasing. In recent years, some clinical trials have shown that autologous bone marrow mesenchymal cells seem to have an effect in the treatment of SCI.<sup>33,34</sup>

**CONCLUSIONS**

Research on stem cells for SCI is a well-developed and promising research field. Literature has been increasing yearly in the last 2 decades. *Cell Transplantation*, *Journal of Neurotrauma*, *Neural Regeneration Research*, and *Experimental Neurology* show more interest in this field. H. Okano, the University of Toronto, and the

United States were the top author, institution, and country, respectively. Researchers and institutions from Canada, the United States, Japan, and China contributed most in this field. Global research collaborations have been broad, but more cooperation between top authors, institutions, and countries may be needed.

**Limitations**

Some limitations should be noted from our study. First, literature not recorded in the WoS Core Collection was not included.

Therefore, our findings may not be comprehensive. Besides, although the search criteria defined the topic of the studies, we cannot guarantee that each document was completely relevant to

the topic. Third, self-reference bias was not considered in our study. However, we believe that this study can still be used to describe the overall situation and general trend in this field.

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