

Research Paper

Bibliometric Analysis of Stem Cells in Ischemic Stroke (2001–2022): Trends, Hotspots and Prospects

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Abstract

Background: Ischemic stroke is a common cerebrovascular accident with a high risk of neurological deficits. Stem cell therapy has progressively attracted the interest of scientists and clinicians due to the benefits of promoting neural regeneration and regulating the microenvironment surrounding the lesion after ischemic stroke. Our study aimed to evaluate the development trends and research hotspots in the field of stem cells and ischemic stroke.

Materials and methods: Publications related to stem cells and ischemic stroke were retrieved from the Web of Science from 2001 to 2022. Data analysis and mapping were performed using VOSviewer, Citespace and ImageGP.

Results: In total, 1932 papers were included in the analysis. Publications have steadily increased over the past 22 years. China has contributed the maximum number of publications, whereas the USA ranked first in the total number of citations and was considered the center of the international collaboration network. University of South Florida, Henry Ford Hospital, and Oakland University were the most influential institutions. Stroke, Brain Research, and Neural Regeneration Research were the most productive journals. The research in this field was primarily focused on the effects of stem cells on neurogenesis, inflammation, and angiogenesis following ischemic stroke, as well as their therapeutic potential for the disease. In addition, neural stem cells and mesenchymal stem cells are the most commonly utilized stem cells. The topics related to miRNA, extracellular vesicles, exosomes, mesenchymal stem cells, neuroinflammation, and autophagy are current research hotspots.

Conclusion: Our bibliometric study provides a novel perspective on the research trends in the field of stem cells and ischemic stroke. The outcome of this study may benefit scientists to identify research hotspots and development directions, thereby advancing the application of stem cell-based therapy for ischemic stroke.

Keywords: Ischemic stroke; Stem cells; Bibliometric analysis; Neurogenesis; Paracrine effects; Translation.

Introduction

Ischemic stroke accounts for approximately 80% of stroke incidences and is caused by decreased cerebral blood flow with a subsequent reduction of

oxygen and glucose, leading to localized cerebral ischemic necrosis or softening and corresponding impairment of neurological functions [1]. It is one of

the leading causes of death and disability worldwide [2]. Currently, tissue plasminogen activator is the only drug approved by the Food and Drug Administration (FDA, USA) to treat acute ischemic stroke. However, the narrow time windows and high risk of haemorrhage limit the benefit to patients [3]. It is urgently required for the exploration of novel alternative therapies with improved efficacy to reduce mortality and restore neurological deficits following ischemic stroke. Despite the fact that ischemic stroke can induce neurogenesis, angiogenesis, axonal sprouting, and synaptic plasticity, the sporadic endogenous repair is insufficient to compensate for the neurological defect [4]. Stem cell-based therapy is an emerging therapy for neurological recovery after ischemic stroke. It is postulated to modulate neuroinflammation, augment or complement endogenous repair, and reconstruct the neural circuits [5, 6].

Previous research has indicated that stem cell-based therapy is an effective method for promoting neural function recovery after ischemic stroke. Zhang et al. demonstrated that the proliferation of neural precursor cells (NPCs) in the subventricular zone (SVZ) was observed within 2 weeks after focal ischemic stroke, and that the number of NPCs decreased substantially after 4 weeks [7]. The transient increase of NPCs implies an endogenous window of neuroplasticity, which offers an opportunity to improve the prognosis of ischemic stroke. Mesenchymal stem cells (MSCs), are the most extensively distributed adult stem cells and serve as

an excellent therapeutic agent for the treatment of ischemic stroke [8]. The neuroprotective effect of MSCs is associated with the release of bioactive substances [9]. Transfection of brain-derived neurotrophic factor and placental growth factor with MSCs substantially enhanced the neurological function of ischemic rats [10, 11]. Furthermore, circulating endothelial progenitor cells (EPCs) and vascular progenitor cells (VPCs) contribute to neovascularization after stroke [12, 13], while tumorigenicity limits the clinical application of embryonic stem cells (ESCs) and induced pluripotent stem cells (iPSCs) [14, 15]. With the progress of stem cell research, various stem cells have been used in the preclinical study of ischemic stroke [16, 17]. In addition, 86 clinical trials involving the use of stem cells to treat ischemic stroke demonstrate the potential of stem cell-based therapy in clinical settings (*clinicaltrials.gov*, accessed Sep 15, 2023). Recently, the immunomodulatory properties and beneficial paracrine effects of stem cells in ischemic stroke have garnered considerable interest [18, 19]. Increased emphasis on this field has resulted in the accelerated growth of the number of publications. We summarized the influential literature related to stem cells for ischemic stroke treatment over the past 22 years, as shown in **Figure 1**. In this study, we integrated all the published literature on stem cells and ischemic stroke research, and identified research trends and hotspots in the field, which are anticipated to provide future development prospect.

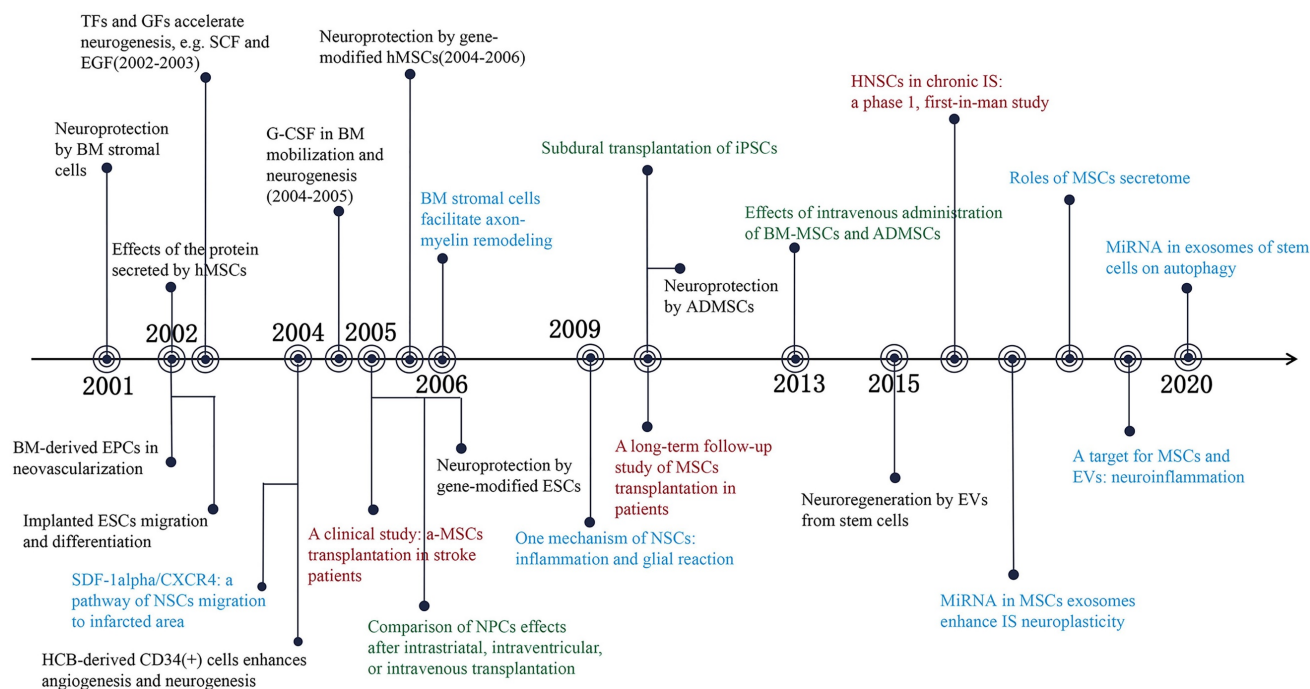


Figure 1. Significant findings of stem cells and ischemic stroke during 2001-2022. Events in black present observation research; Events in blue mean mechanism research; Events in red indicate clinical trials and events in green refer to transplantation routes of stem cells. BM: Bone marrow; hMSCs: Human mesenchymal stem cells; EPCs: Endothelial

progenitor cells; ESCs: Embryonic stem cells; TFs: Trophic factors; GFs: Growth factors; SCF: Stem cell factor; EGF: Epidermal growth factor; SDF-1 α : Stromal cell-derived factor 1 α ; CXCR4: CXC chemokine receptor 4; NSCs: Neural stem cells; HCB: Human cord blood; G-CSF: Granulocyte-colony stimulating factor; NPCs: Neural precursor cells; iPSCs: Inducible pluripotent stem cells; ADMSCs: Adipose derived mesenchymal stem cells; EVs: Extracellular vehicles; HNSCs: Human neural stem cells; IS: Ischemic stroke. (References were displayed on **Table S1**.)

Bibliometric analysis is a statistical tool that provides an overview of a specific scientific research field, describes the research trends, and predicts the prospective future directions through qualitative and quantitative approaches [20]. In recent years, bibliometric analysis has been extensively used in stem cell research and the field of neuroscience [21-23]. In this study, we performed a bibliometric study of the literature on stem cells and ischemic stroke published between 2001 and 2022. This bibliometric study evaluated the publication trends, countries, institutions, journals, high-cited articles, references and keywords based on basic bibliometric indicators, co-authorship networks, co-citation analysis and co-occurrence of author keywords. The mapping analysis illustrated the research trends in the field, the topics of greatest concern, and potential future research directions.

Materials and Methods

Data source and search strategy

The data was retrieved from the Web of Science (WoS) core collection, including the Science Citation Index-expanded (SCI-E) and Social Sciences Citation Index (SSCI), which is generally regarded as the most popular database for bibliometric analysis [24]. The year of publications was from 2001 to 2022, and document types were limited to original articles and reviews (**Figure 2**). The searched criteria were

displayed in **Table S2**. A total of 1932 published papers were retrieved and exported in the form of all records and references.

Data standardization

Data standardization was performed on keywords and institutions in our study. The processing principles on keywords were the following: (1) Merging synonymous terms, e.g., “brain ischemia” and “cerebral ischemia”; (2) Acronyms were generally preferable, e.g., “MCAO” for “middle cerebral arterial occlusion”, similarly, “blood brain barrier” was abbreviated for “BBB”; (3) The singular and plural forms of the identical noun (e.g., Stem cell and Stem cells) were unified. The processing principles on institutions were the following: (1) Unifying the nomenclature of an institution, e.g., “Zhejiang univ affiliated hosp 2” and “Hosp 2 zhejiang univ” were unified to “Zhejiang univ hosp 2”; (2) The abbreviation was unified as the full name, e.g., “Nimh” were standardized to “National Institute of Mental Health”.

Data analysis

Four indicators were adopted to evaluate the productivity and impact of research publications as follows: total publications (TP), total citations (TC), average citation per publication (ACPP), and H-index (which denotes that an entity has H publications, each of which has been cited a minimum of H times by

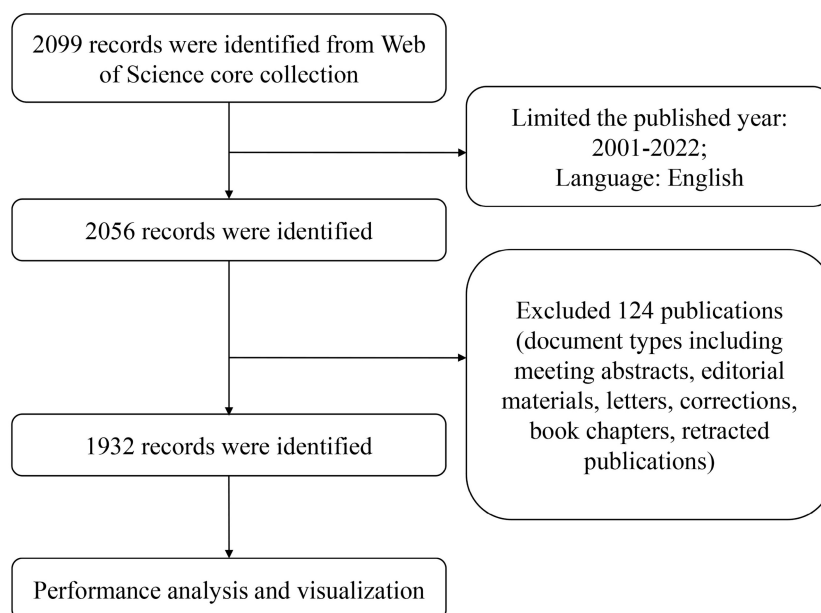


Figure 2. Flow diagram of publications screening.

other articles) [24]. These indicators reflected the academic impact of a country, an institution or a journal.

VOSviewer is a well-known and optimal tool for creating and viewing bibliometric maps. In this study, VOSviewer (version 1.6.18) was used for country and institution cooperation analysis and keyword co-occurrence analysis. A measurement index clustering technique was used in the software to categorise the keywords into distinct clusters based on their association intensity and direction, and simultaneously represented each cluster by colour and time progression with varying shades [25].

CiteSpace (version 6.2.R1) was used to perform co-citation analysis of references and citation burst detection [26]. The time slicing was selected from January 2001 to December 2022. Years per slice was picked by one. The selection criteria were set as follows: g-index (k=5), link retaining factor (LRF) =3.0, maximum links per node (L/N) =10, look back year (LBY) =5, e =1.0. The rest of the parameters were selected by default setting. For clustering analysis, we adapted clustering algorithms based on keywords and log-likelihood ratio (LLR) to group the literatures into conceptual clusters with different research characteristics and label each cluster with noun phrase. The colours of the clusters were determined by citing years.

ImageGP, an online data visualization tool based on R programming language [27], was employed to characterize the temporal trend of high frequency keywords in the field of stem cells and ischemic stroke.

Results

Timeline distribution of publications

Figure 3 shows the temporal development trend in the field of stem cells and ischemic stroke over time. In the past 22 years, the number of publications has increased steadily, reaching 143 papers in 2022, which is 13 times the number published in 2001 (11 papers). This indicates that researchers have become increasingly interested in the fields of stem cells and ischemic stroke. The frequency of total citations fluctuated prior to 2005, peaked in 2006 (7162 times), and then declined progressively from 2017 to 2022. The average number of citations per paper dropped by 99.0% from 156.55 in 2001 to 1.49 in 2022.

Analysis of countries distribution

In our database, 61 countries were identified. Countries with at least 5 publications were shown in Figure 4A. The main participating countries are distributed in the USA, China, South Korea, Japan and Germany. China contributed the most papers (752

papers, 38.92%) and the USA ranked first place in the total number of citations (36921) (Table 1). The USA had highest average number of citations per article (73.11), followed by Canada (63.75) and Germany (60.30). Overall, top 10 countries contributed 90.48% of all publications.

Table 1. Top 10 most productive countries in the field of stem cells and ischemic stroke.

Rank	Country	TP	Percentage (%)	TC	ACPP	H-index
1	China	752	38.92	17581	23.38	59
2	USA	505	26.14	36921	73.11	100
3	Japan	253	13.10	11273	44.56	60
4	South Korea	150	7.76	7648	50.99	42
5	Germany	133	6.88	8020	60.30	44
6	UK	70	3.62	3538	50.54	33
7	Canada	52	2.69	3315	63.75	29
8	Italy	51	2.63	2864	56.16	26
9	Spain	44	2.28	1544	35.09	24
10	France	44	2.28	1360	30.91	22

TP: total publications; TC: total citations; ACPP: average citation per publication.

Subsequently, we analysed the growth trend of top 5 productive countries during the last 22 years (Figure 4B). USA and Japan were the most prolific countries before 2007, after which the number of publications in USA exhibited a fluctuating growth pattern whereas the growth rate in Japan was sluggish. Despite China's late entry into in this field, the number of published articles increased swiftly. After surpassing the USA in 2013, China has maintained a consistent upward trend in the number of publications over the years. In South Korea and Germany, the number of publications has been at a low.

To explore the characteristics of cooperation among countries in this field, we illustrated a collaboration network including countries with at least 5 publications (Figure 4C). Among 31 countries, there are 19 from Europe, 7 from Asia Pacific, 2 from the Middle East and North Africa, 2 from North America and 1 from South America. USA is at the centre of the international cooperation network, maintains deep relations with other prominent countries in this field, and has the most connections to China (87 times). However, the majority of countries lack stable and comprehensive communication and cooperation.

Analysis of institutions distribution

We identified the 10 most productive and influential institutions in the field of stem cells and ischemic stroke, as shown in Table 2. University of South Florida (45 papers) was the most prolific institution, followed by Henry Ford Hospital (34 papers) and Oakland University (33 papers). In terms of total citations, Henry Ford Hospital topped the list with 4450 citations, followed by Oakland University

(4414 citations). Overall, 4 of top 10 institutions were from the USA, while China, South Korea, and Japan each had two institutions.

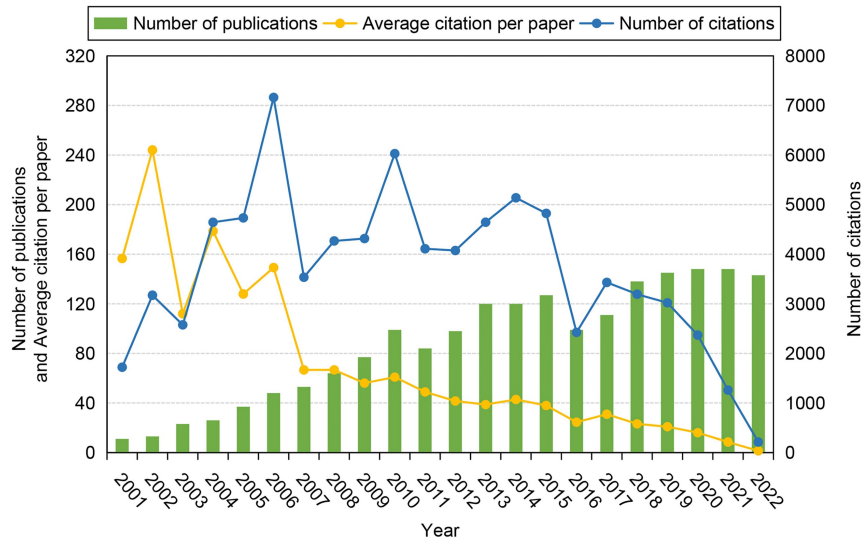


Figure 3. Timeline distribution of publications in the field of stem cells and ischemic stroke during 2001-2022.

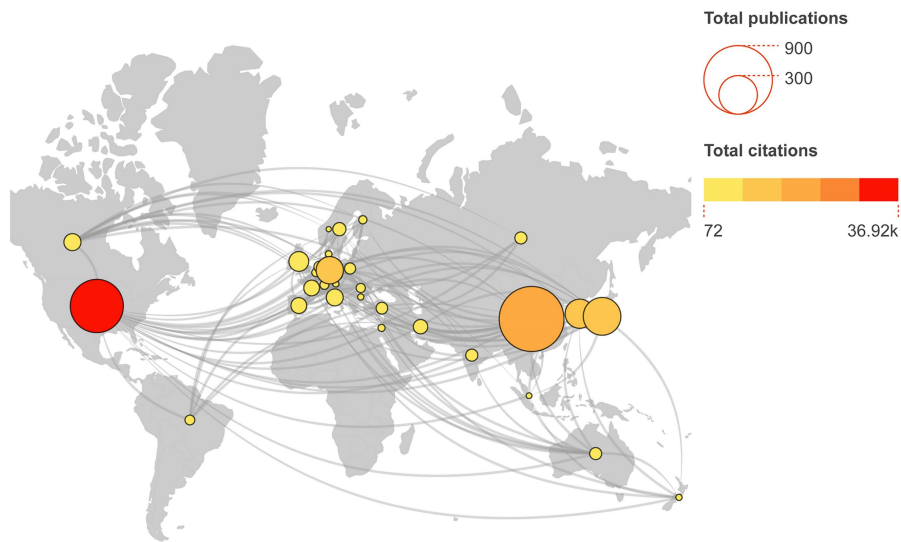


Figure 4A. Global collaboration and distribution of publications in the field of stem cells and ischemic stroke. The number of publications and total citations are represented, accordingly, by node sizes and colours.

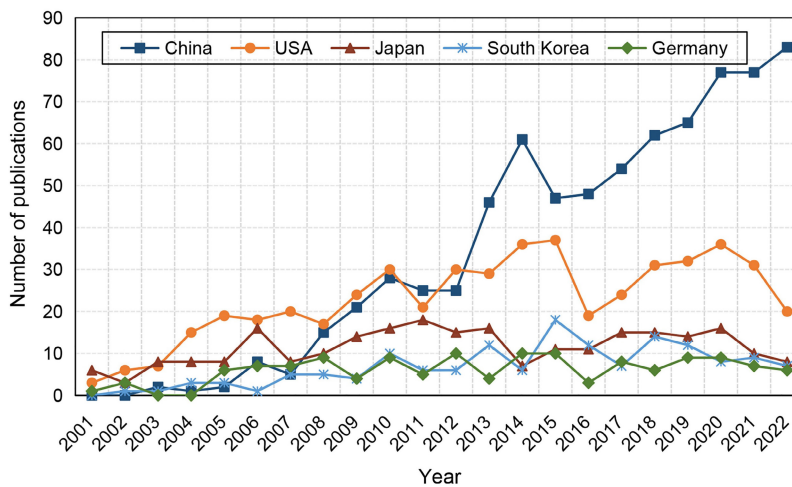


Figure 4B. Top 5 countries distribution trends of publications in the field of stem cells and ischemic stroke.

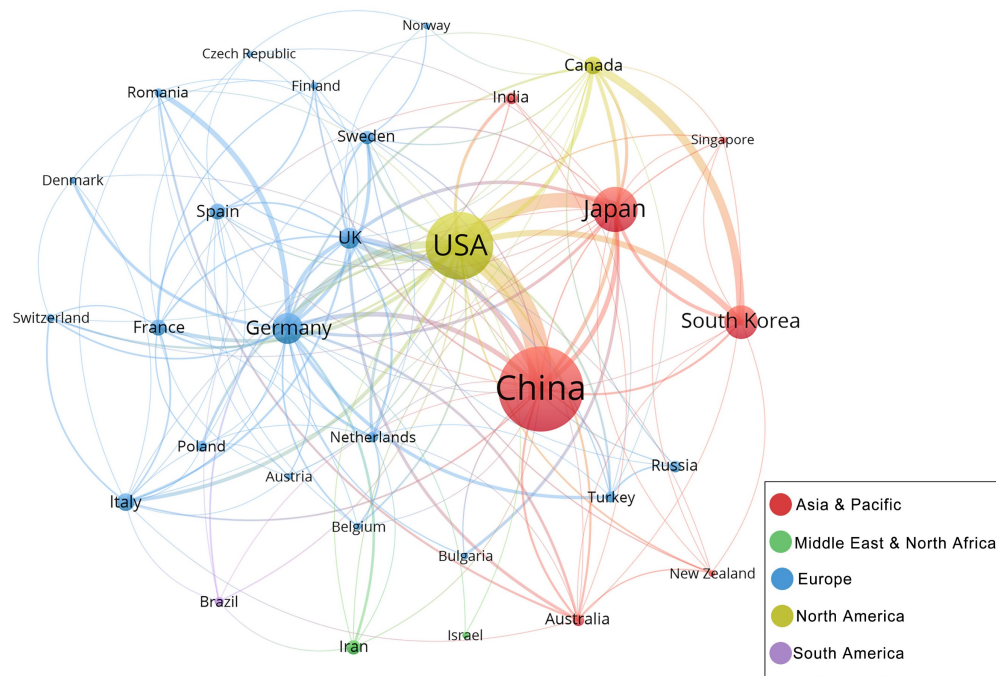


Figure 4C. Collaboration networks of the countries with at least 5 publications. Nodes in the network denote countries, and the size of nodes hinges on the number of publications of countries; The curves represent the linkages between different countries, and the size depends on the intensity of cooperation; The colours represent regional distribution.

Table 2. Top 10 most productive institutions in the field of stem cells and ischemic stroke.

Rank	Institution	Country	TP	TC	ACPP	H-index
1	University of South Florida	USA	45	1426	31.69	20
2	Henry Ford Hospital	USA	34	4450	130.88	29
3	Oakland University	USA	33	4414	133.76	28
4	Shanghai Jiao Tong University	China	32	1166	36.44	17
5	Yale University	USA	30	1905	63.50	19
6	Shanghai Jiao Tong University Ruijin Hospital	China	29	1500	51.72	20
7	Hyogo College of Medicine	Japan	28	1773	63.32	17
8	Yonsei University	South Korea	27	2604	96.44	17
9	Sapporo Medical University	Japan	26	2601	100.04	20
10	Sungkyunkwan University	South Korea	26	885	34.04	17

TP: total publications; TC: total citations; ACPP: average citation per publication.

Next, we analysed the partnerships among institutions involved in this field. **Figure 5** illustrates a collaborative network that includes 151 institutions with 7 or more publications. Most of the close partnerships between institutions are from the same country, such as Oakland University and Henry Ford Hospital in the USA with 33 links, and Shanghai Jiao Tong University and Shanghai Jiao Tong University Ruijin Hospital in China with 20 links. Among transnational cooperations, Yale University, USA and Sapporo Medical University, Japan has the closest connections, and they have collaborated to publish 21 articles. In this network, 61 institutions (40.40%) come from China and 28 institutions (18.54%) from USA.

Analysis of influential journals

537 academic journals have published articles pertaining to stem cells and ischemic stroke. The

number of publications of top 10 journals in the field accounted for 24.28% (469 out of 1,932) of the total publications, as shown in **Table 3**. Stroke ranked first in all metrics, including the number of publications, total citations, citations per publication, H-index and impact factor, reflecting its preeminent position in the field. The second and third most productive journals were Brain Research and Neural Regeneration Research. Stroke and Journal of Cerebral Blood Flow and Metabolism had a total citation frequency greater than 3000. The impact factor of more than half of the top 10 journals was greater than 5. Moreover, these journals were predominantly distributed in the field of neuroscience.

Analysis of highly cited articles

Top 10 articles with the highest citations on stem cells and ischemic stroke are shown in **Table 4**. Three articles with citation frequency above 800 were published in Journal of Cellular Biochemistry, Proceedings of the National Academy of Sciences of the United States of America, and Annals of Neurology, respectively. The article with the greatest citation frequency (2120 citations) was titled “Mesenchymal stem cells as trophic mediators” and written by Caplan in 2006. The latest publication with 557 citations was “A long-term follow-up study of intravenous autologous mesenchymal stem cell transplantation in patients with ischemic stroke”, published in Stem Cells in 2010.

Analysis of co-cited references

The structure and dynamics of a knowledge domain are reflected in reference co-citation analysis, which also reveals the research frontiers and knowledge base [28]. A total of 1182 co-cited references were identified on research of stem cells and ischemic stroke over the last 22 years. **Figure 6** displays 343 co-cited references obtained from the top 30 co-cited references per time slice for 2000-2022. The most co-cited reference was performed by Arvidsson A et al. in 2002. The article with highest centrality (0.77) was titled "Intravenous bone marrow stem cell grafts preferentially migrate to spleen and abrogate chronic inflammation in stroke" and published in Stroke in 2015. **Table 5** presented more details on top 10 references cited. All of references were co-cited at least 28 times. The most co-cited reference was an original article published in Nature Medicine, entitled "Neuronal replacement from endogenous precursors in the adult brain after stroke".

As shown in **Figure 6**, we further recognized 15 clusters with different colours and size, which

indicates that 15 different research topics have been concentrated in the field of stem cells and ischemic stroke in the past 22 years. #0 "pluripotent stem cells" and #1 "neural progenitor cells" are larger clusters. #0 includes 30 papers, primarily focusing on the efficacy and underlying mechanisms of different types of stem cells in the context of treating ischemic stroke. #1 comprises a collection of 28 papers that mostly centred around the transplantation of neural progenitor cells. These articles explored various transplantation methods, such as intravenous transplantation, intra-arterial transplantation, and intracerebral injection, among others. #10 "hematopoietic growth factor", #9 "hippocampus", #13 "bone marrow", #2 "neurogenesis" were earlier research topics in this field. #8 "exosomes" and #3 "ischemic stroke" presented the latest hotspots. Among cluster emerging in recent years, the number of articles in #15 "clinical trials" was relatively small, which reflected that the correspondent research was not yet mature.

Table 3. Top 10 most productive journals in the field of stem cells and ischemic stroke.

Rank	Journal	TP	TC	ACPP	H-index	IF (2021)	WOS category (rank/total number of journals in WOS category)
1	Stroke	59	5351	90.69	40	10.17	Clinical Neurology (14/212) Peripheral Vascular Disease (7/67)
2	Brain Research	58	2682	46.24	31	3.61	Neurosciences (156/275)
3	Neural Regeneration Research	57	873	15.32	16	6.058	Cell Biology (69/195) Neurosciences (61/275)
4	Cell Transplantation	56	1944	34.71	25	4.139	Cell & Tissue Engineering (19/29) Medicine, Research & Experimental (75/139) Transplantation (9/25)
5	PLoS One	52	2433	46.79	28	3.752	Multidisciplinary Sciences (29/74)
6	Journal of Cerebral Blood Flow and Metabolism	45	3516	78.13	31	6.597	Endocrinology and Metabolism (26/146) Hematology (20/78) Neurosciences (49/275)
7	Stem Cell Research & Therapy	40	1174	29.35	19	8.088	Cell & Tissue Engineering (4/29) Cell Biology (46/195) Medicine, Research & Experimental (27/139)
8	International Journal of Molecular Sciences	36	586	16.28	12	6.208	Biochemistry & Molecular Biology (69/297) Chemistry, Multidisciplinary (50/179)
9	Neuroscience	33	1903	57.67	21	3.708	Neurosciences (147/275)
10	Experimental Neurology	33	2239	67.85	22	5.62	Neurosciences (72/275)

TP: total publications; TC: total citations; ACPP: average citation per publication; IF: impact factor.

Table 4. Top 10 articles with the highest citations in the field of stem cells and ischemic stroke.

Rank	Year	First Author	Title	Journal	Citations
1	2006	Caplan, A.I.	Mesenchymal stem cells as trophic mediators.	Journal of Cellular Biochemistry	2120
2	2004	Imitola, J.	Directed migration of neural stem cells to sites of CNS injury by the stromal cell derived factor 1 alpha/cxcl12 chemokine receptor 4 pathway.	Proceedings of the National Academy of Sciences of The United States of America	856
3	2005	Bang, O.Y.	Autologous mesenchymal stem cell transplantation in stroke patients.	Annals of Neurology	845
4	2001	Volpe, J.J.	Neurobiology of periventricular leukomalacia in the premature infant.	Pediatric Research	685
5	2006	Ohab, J.J.	A neurovascular niche for neurogenesis after stroke.	Journal of Neuroscience	668
6	2002	Zhao, L.R.	Human bone marrow stem cells exhibit neural phenotypes and ameliorate neurological deficits after grafting into the ischemic brain of rats.	Experimental Neurology	647
7	2004	Taguchi, A.	Administration of cd34(+) cells after stroke enhances neurogenesis via angiogenesis in a mouse model.	Journal of Clinical Investigation	616
8	2002	Hoehn, M.	Monitoring of implanted stem cell migration <i>in vivo</i> : a highly resolved <i>in vivo</i> magnetic resonance imaging investigation of experimental stroke in rat.	Proceedings of the National Academy of Sciences of the United States of America	586
9	2010	Lee, J.S.	A long-term follow-up study of intravenous autologous mesenchymal stem cell transplantation in patients with ischemic stroke.	Stem Cells	557
10	2005	Schneider, A.	The hematopoietic factor g csf is a neuronal ligand that counteracts programmed cell death and drives neurogenesis.	Journal of Clinical Investigation	539

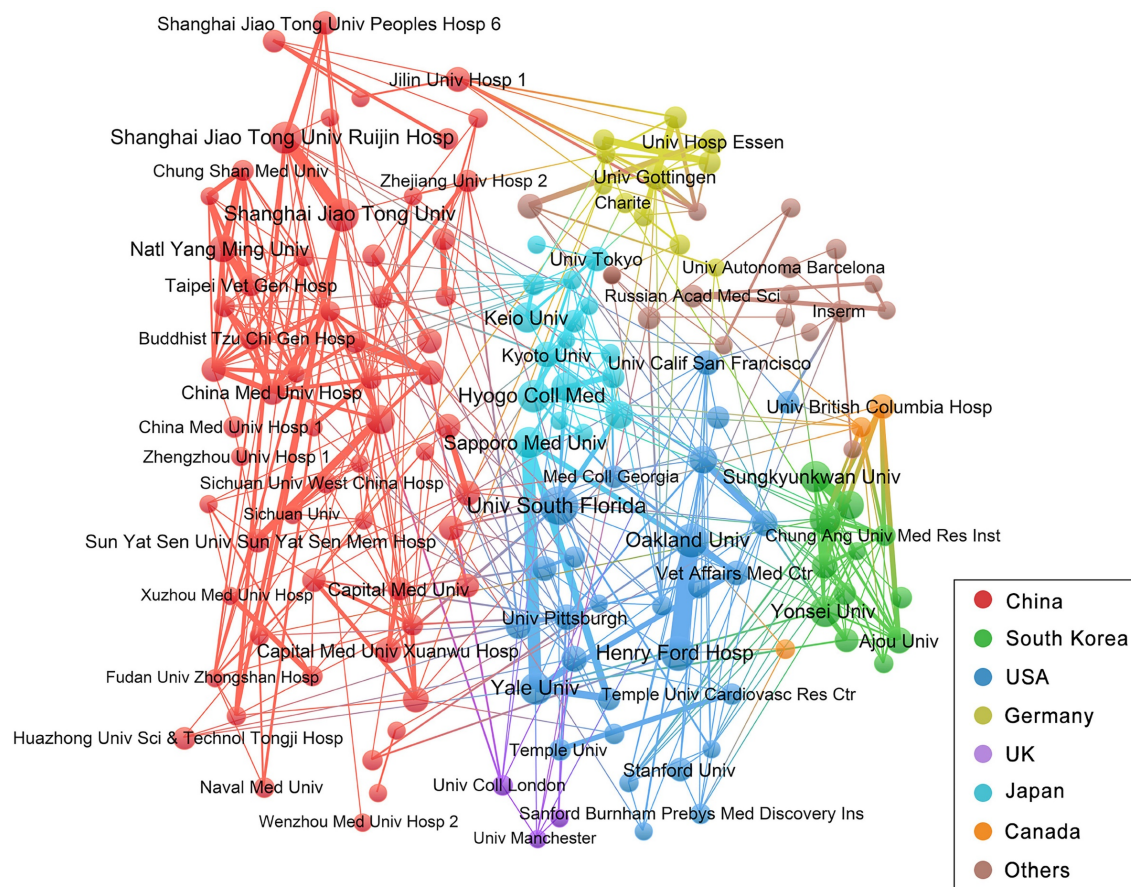


Figure 5. Collaboration networks of the institutions with at least 7 publications. Nodes in the network denote institutions, and the size of nodes hinges on the number of publications of institutions. The lines represent the linkages between different institutions, and the size depends on the intensity of cooperation. The colours represent different countries.

Table 5. Top 10 co-cited references in the field of stem cells and ischemic stroke.

Rank	Title	Journal	Co-citation	Centrality
1	Neuronal replacement from endogenous precursors in the adult brain after stroke (Arvidsson A, 2002).	Nature Medicine	56	0.19
2	A long-term follow-up study of intravenous autologous mesenchymal stem cell transplantation in patients with ischemic stroke (Lee JS, 2010).	Stem Cells	46	0.68
3	Intravenous administration of auto serum-expanded autologous mesenchymal stem cells in stroke (Honmou O, 2011).	Brain	38	0.56
4	Regeneration of hippocampal pyramidal neurons after ischemic brain injury by recruitment of endogenous neural progenitors (Nakatomi H, 2002).	Cell	36	0.01
5	Neurorestorative therapies for stroke: underlying mechanisms and translation to the clinic (Zhang ZG, 2009).	The Lancet. Neurology	34	0
6	Clinical outcomes of transplanted modified bone marrow-derived mesenchymal stem cells in stroke: A phase 1/2a study (Steinberg GK, 2016).	Stroke	31	0.04
7	Subventricular zone-derived neuroblasts migrate and differentiate into mature neurons in the post-stroke adult striatum (Yamashita T, 2006).	The Journal of Neuroscience	30	0.17
8	Neurogenesis in dentate subgranular zone and rostral subventricular zone after focal cerebral ischemia in the rat (Jin KL, 2001).	Proceedings of the National Academy of Sciences of the United States of America	28	0.03
9	Rat forebrain neurogenesis and striatal neuron replacement after focal stroke (Parent JM, 2002).	Annals of Neurology	28	0.2
10	Stem cells for ischemic brain injury: a critical review (Burns TC, 2009).	Journal of Comparative Neurology	28	0.33

Top 20 references with the strongest citation burst were displayed in **Table 6**. Reference citation bursts emerged as early as 2002, and all references had citation burst strengths greater than 10. The reference with the strongest citation burst (strength=26.75) was titled “Neuronal replacement from endogenous neural precursors induced by

ischemic stroke”, published in 2002. The reference burst spanned from 2017 to 2022 and is titled "Clinical outcomes of transplanted modified bone marrow-derived mesenchymal stem cells in stroke: a phase 1/2a Trial," highlighting one of research interests during the last 5 years. Three of the references began to burst after 2017, with the primary

subject of the clinical usage of MSCs, the therapeutic potential of extracellular vehicles (EVs), and the role of miRNA in EVs, respectively. **Table S3** summarizes the main research contents of top 20 references in the order of the literature in **Table 6**.

Analysis of keywords co-occurrence and hotspots

A total of 1,978 keywords were identified in our dataset. We have listed 30 most frequently occurring

keywords in **Table S4**. Higher occurrences of keywords such as NSCs, MSCs, neurogenesis, angiogenesis, apoptosis, and inflammation indicate that they have received considerable attention in the field. Furthermore, **Figure 7** presents the top 20 stem cell types most frequently used in research on ischemic stroke. The figure shows that NSCs and MSCs are the most commonly recognized stem cells.

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 WoS: D:\Scientific Research\stem cells and ischemic stroke\2001-2022\Citespace\data\data
 Timespan: 2001-2022 (Slice Length=1)
 Selection Criteria: g-index (k=5), LRF=3.0, L/N=10, LBY=5, e=1.0
 Network: N=343, E=425 (Density=0.0072)
 Largest CC: 324 (94%)
 Nodes Labeled: 1.0%
 Pruning: Pathfinder
 Modularity Q=0.8627
 Weighted Mean Silhouette S=0.9659
 Harmonic Mean(Q, S)=0.9114

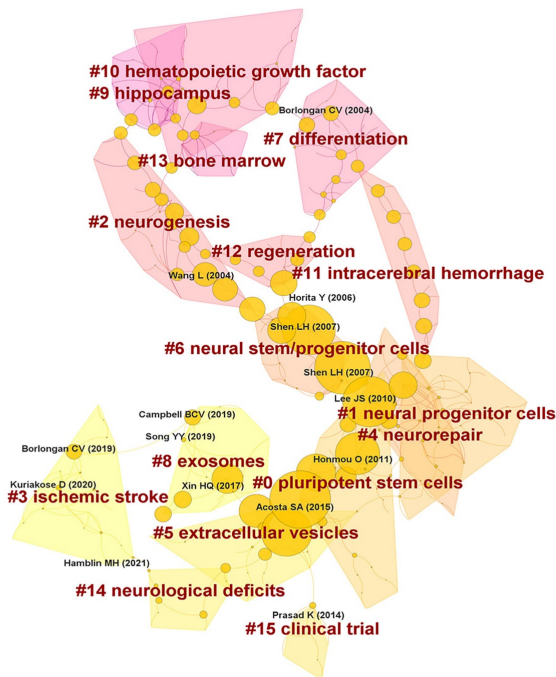
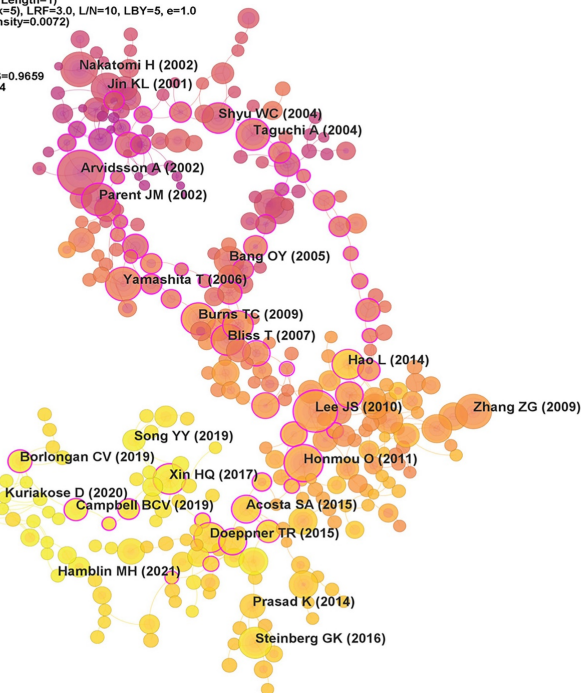


Figure 6. Visualization map of co-cited references and clustering network. In the left image, each circle represents a reference and the size of a circle is proportional to the citation frequency. The purple nodes reflect older references, whereas the yellow nodes represent more recent references. The betweenness centrality is denoted by a purple circle around each node. In the right image, each circle represents a reference and the size of a circle is proportional to the betweenness centrality.

Table 6. Top 20 references with the strongest citation bursts in stem cells and ischemic stroke research.

Rank	First Author	Year	Strength	Begin	End	2001-2022
1	Chen JL [29]	2001	10.66	2002	2006	
2	Arvidsson A [30]	2002	26.75	2003	2007	
3	Nakatomi H [31]	2002	17.02	2003	2007	
4	Jin KL [32]	2001	14.67	2003	2006	
5	Parent JM [33]	2002	13.85	2004	2007	
6	Li Y [34]	2002	11.85	2004	2007	
7	Shyu WC [35]	2004	12.25	2005	2008	
8	Taguchi A [36]	2004	11.84	2005	2009	
9	Bang OY [37]	2005	12.39	2007	2010	
10	Yamashita T [38]	2006	15.13	2008	2011	
11	Bliss T [39]	2007	12.31	2009	2012	
12	Burns TC [40]	2009	11.28	2010	2014	
13	Lee JS [41]	2010	19.21	2011	2015	
14	Zhang ZG [42]	2009	15.63	2011	2014	
15	Honmou O [43]	2011	16.43	2012	2016	
16	Hao L [44]	2014	12.96	2015	2019	
17	Cotten CM [45]	2014	10.94	2015	2019	
18	Steinberg GK [46]	2016	14.32	2017	2022	
19	Doepfner IR [47]	2015	13.67	2018	2020	
20	Xin HQ [48]	2017	13.00	2020	2022	

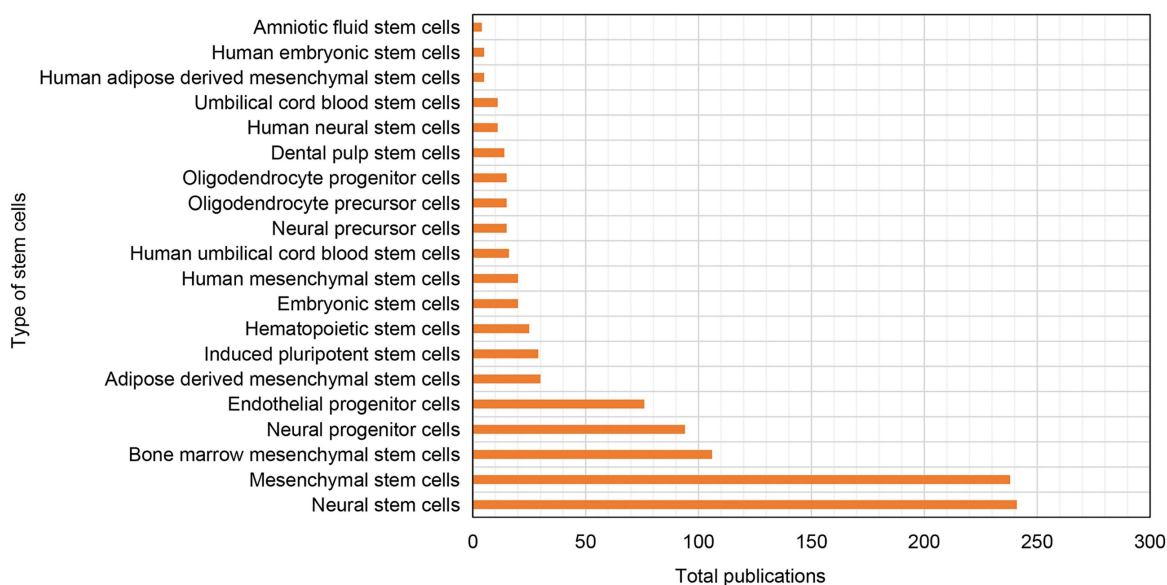


Figure 7. Top 20 most widely used stem cell types in the research of ischemic stroke.

The co-occurrence network was constructed using 116 keywords with at least 20 occurrences, as shown in **Figure 8**. The keywords in the network were divided into 6 clusters. Cluster 1 (red) focuses on the interaction between stem cells and neural cells after ischemic stroke, including keywords such as cell differentiation, neurons, astrocyte, microglia, oligodendrocytes, etc. Cluster 2 (green) shows extensive application and mechanism of MSCs in ischemic stroke, including preclinical studies and clinical trials. Cluster 3 (blue) and cluster 5 (purple) describe the effects of stem cells on inflammation and neuroprotection after ischemic stroke, with keywords such as oxidative stress, apoptosis, cell death, blood brain barrier (BBB), etc. Cluster 4 (yellow) focuses on the role of stem cells in neurogenesis following ischemic stroke, including keywords such as neural progenitor cells, nerve regeneration, subventricular zone, dentate gyrus, etc. Cluster 6 (bright blue) shows the role of stem cells in angiogenesis and the signalling molecules involved, such as the keywords endothelial progenitor cells, vascular endothelial growth factor (VEGF), etc.

As shown in **Figure 9**, VOSviewer assigned distinct colours to keywords based on their average appearance year (AAY). In the image, blue keywords appeared before yellow ones. The keywords miRNA, EVs, exosomes, autophagy, neuroinflammation, and oxidative stress are recent hotspots. Finally, we performed a heat map analysis of time trends for the top 30 keywords (**Figure 10**). The role of MSCs in ischemic stroke has attracted the most attention in recent years.

Discussion

General status and scientific impact of research

In this study, we performed a bibliometric analysis of stem cells and ischemic stroke from 2001 to 2022 based on social network analysis software, presenting the research trends and progress in the field. The temporal analysis described the substantial increase in scientific output over the last 22 years. From 2001 to 2010, there was a significant increase in the number of publications, with the number of papers in 2010 being 9 times greater than that in 2001. Tremendous growth in publication suggests significant advancements in the field of stem cells and ischemic stroke in this period. However, growth rate was decelerated after 2010 and the number of publications remained steady, suggesting that the topic continues to receive great attention.

The combined publications of China and the USA constitute 60.56% of the total, which indicates a great contribution to this field by these two countries. In particular, China has published 752 papers (38.92% of total publication). It attributes to the significance of stem cell and ischemic stroke research within USA and China. In co-authorship analysis of countries, USA showed extensive cooperation with various countries, including China, Japan, and the UK. While China exhibited a higher degree of collaboration with USA as compared to other countries. This observation revealed that researchers in the United States put greater emphasis on transnational collaborative endeavors.

hippocampus played an essential role in the initial stage to explore endogenous nerve regeneration in ischemic stroke. Therefore, understanding the mechanisms behind nerve regeneration following cerebral ischemia and identifying strategies to modulate functional neuronal regeneration have emerged as primary areas of early research. These findings offered a theoretical foundation for the application of both endogenous and exogenous stem cells transplantation.

The late research topics include #3 “ischemic stroke”, #5 “extracellular vesicles”, #8 “exosomes” and #15 “clinical trials”, illustrating the areas of focus in recent years. As stem cells transplantation has become progressively developed, several related side effects have emerged such as carcinogenicity, suboptimal transplantation efficiency, and vascular embolism [15, 51]. In contrast, extracellular vesicles (EVs) derived from stem cells as a cell-free therapy have notable clinical advantages like latent tumorigenicity, low survival rate, and immune rejection of transplanted cells. In recent years, researchers in the field have displayed considerable

interest in the therapeutic application potential of EVs.

#0 “pluripotent stem cells” and #1 “neural progenitor cells” are the largest clusters and prominent focus in the field of stem cells and ischemic stroke. #0 contains a diverse array of stem cell categories, with a specific emphasis on evaluating the efficacy and potential mechanisms underlying stem cells transplantation for ischemic stroke. Major stem cell types addressed within this cluster include bone marrow stromal cells, bone marrow MSCs, and EPCs, among others, which suggests that these particular stem cells have been extensively used in the treatment of ischemic stroke [52]. Their safety, feasibility, and efficacy have been partially validated by animal experiments, thus exhibiting significant potential for clinical adoption. #1 primarily concerns evaluating the effectiveness of transplanting neural progenitor cells as a therapeutic approach for ischemic stroke. Neural stem/progenitor cells are well recognized as a vital cellular resource for the application of cell therapy for ischemic stroke. The selection of the stem cell transplantation route significantly influences the

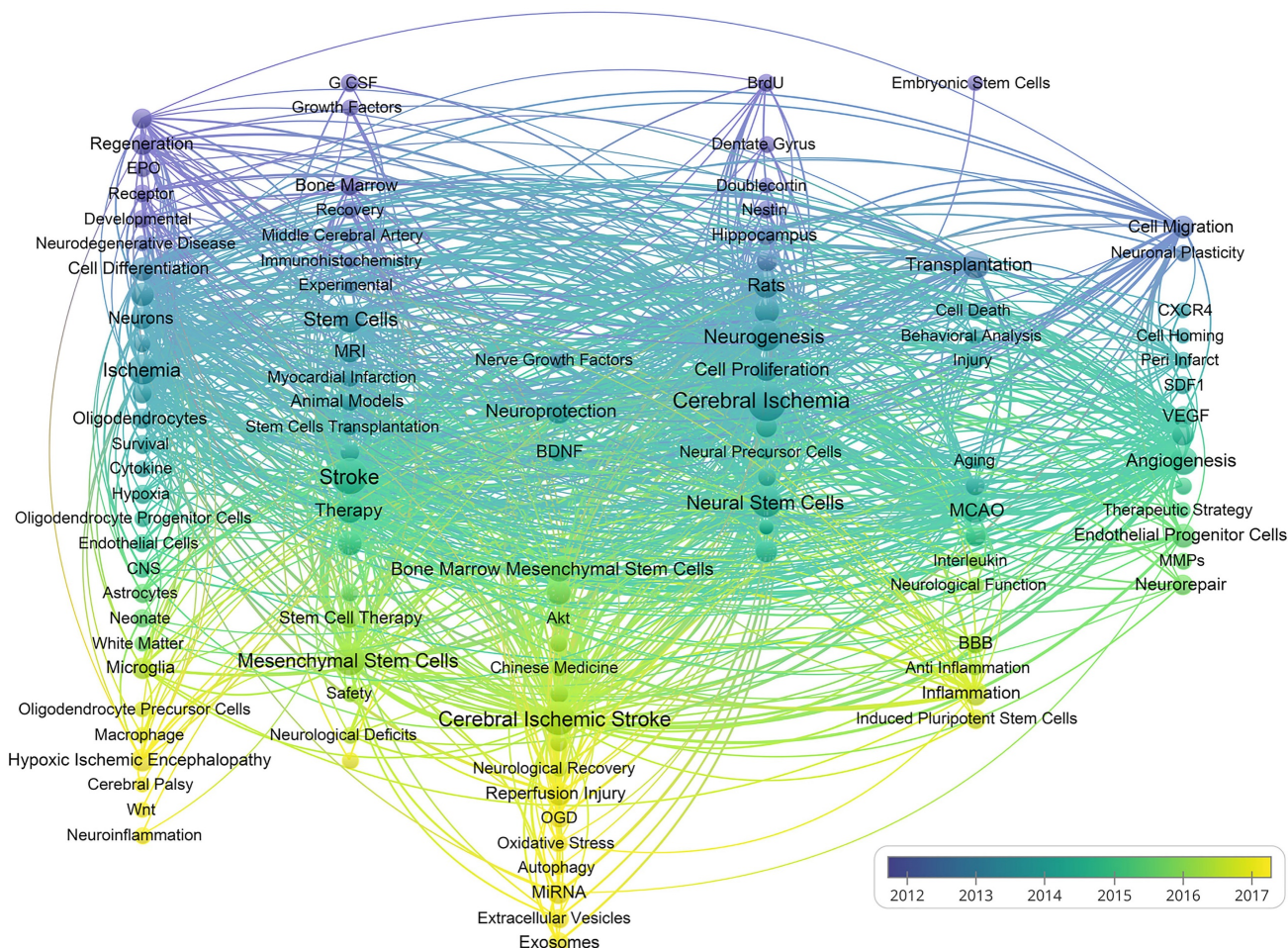


Figure 9. A chronological overview of the co-occurrence map of author keywords based on average appearance year.

safety and efficacy of the therapeutic intervention. Several studies have been conducted to explore different transplantation routes, including vein transplantation, intra-arterial transplantation, and intracerebral injection [53, 54]. By identifying the optimal transplantation pathway, it is possible to enhance nerve regeneration following ischemic stroke and ensure the viability of the donated cells.

Research focus and frontiers

According to major research contents of references with strong citations bursts (Table 6 and Table S3), we can find modified MSCs transplantation in patients, EVs protective function and exosomes application enriched with miRNA cluster have received great attention in the last five years. In keywords occurrence analysis (Figure 8 and Figure 9), we discussed the role of stem cells in ischemic stroke and mostly centered around the following aspects.

Stem cells in neurogenesis after ischemic stroke

Based on clustering analysis, it is evident that nerve regeneration has been a prominent and enduring topic of interest over the course of research. Currently, the efforts to induce neurogenesis after ischemic stroke primarily focused on endogenous

neurogenesis stimulation and exogenous stem cell transplantation. Drugs such as P53 inhibitors, specific neurotrophic factors and peptides have been known to promote the proliferation and migration of NPCs in SVZ and enhance endogenous neurogenesis [55, 56]. In addition, engineered biomaterials have been used to regulate drug release, stem cells reactivity and biochemical cues, which has significant therapeutic potential in neural regeneration [57]. NSCs or NSCs derived from other stem cells compensated directly for the lack of endogenous neural regeneration. Several primary sources of NSCs have been utilized extensively in ischemic stroke research: a) NSCs extracted from fetal brains; b) NSCs derived from ESCs (ESC-NSC); and c) NSCs derived from iPSCs (iPSC-NSC) [58, 59]. Despite several preclinical and clinical studies, it remains greatly challenging to maintain cell viability and regulate cell differentiation for NSC transplantation [60]. Microenvironmental preconditioning, genetic modification, and the biomaterial assistance of NSCs have been applied to reverse the dilemma [61]. Korshunova et al. proposed that gene editing techniques could inhibit the apoptosis of transplanted stem cells [62]. Engineering NSCs to promote post-stroke rehabilitation bears promise for future treatment options [63].

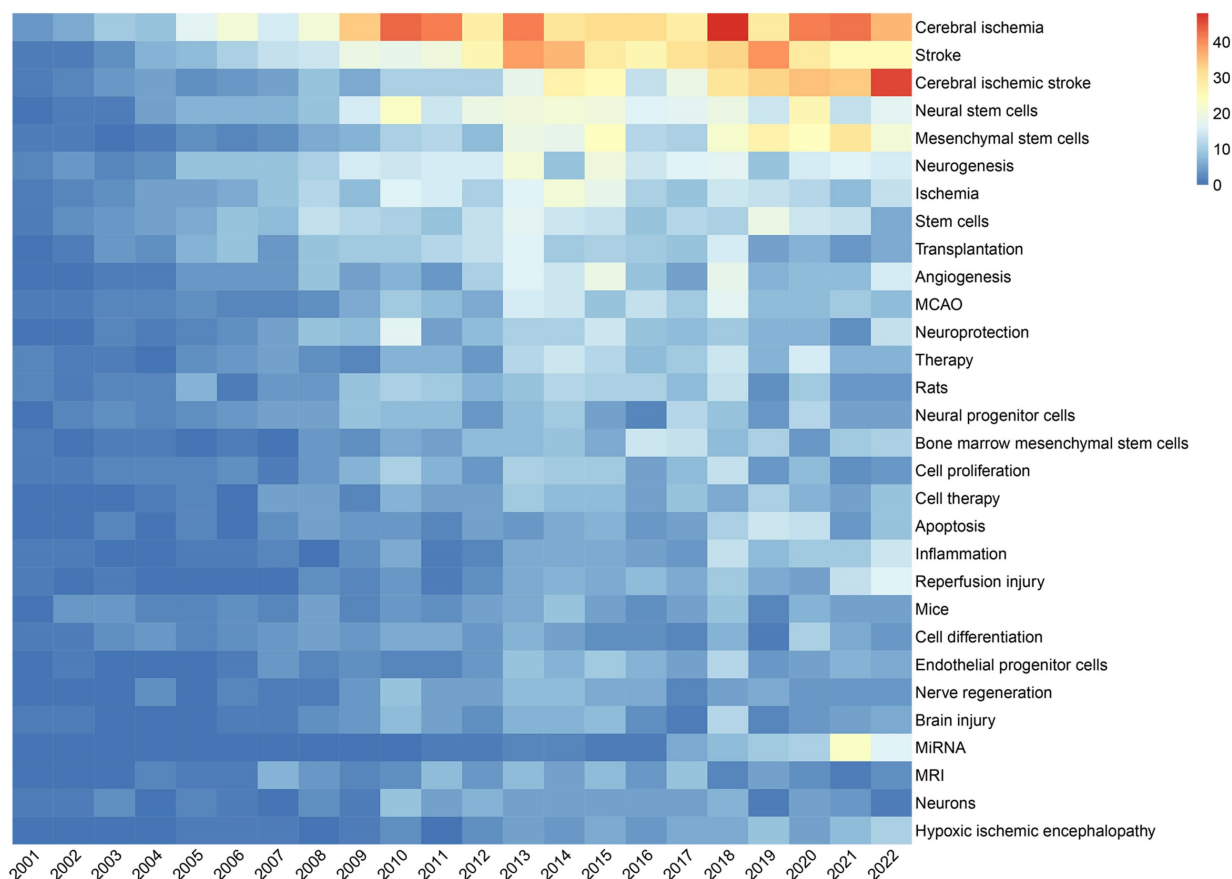


Figure 10. Trend of top 30 the most frequent keywords in stem cells and ischemic stroke research.

Stem cells in inflammation after ischemic stroke

As shown in Table 4, Imitola et al. demonstrated that inflammation guides the behavior of NSCs and recruits these cells to improve neurological deficits after brain ischemia [64]. The article has been cited 856 times, suggesting it as the second most frequently cited paper among top 10 publications. It indicates that inflammatory responses have attracted significant attention of researchers in this field. In keyword clustering analysis (Figure 8), it was observed that "inflammation" was prominent keyword inside cluster 5 (purple). Additionally, cluster 3 (blue) includes the terms "oxidative stress," "apoptosis," and "cell death," which exhibit a strong correlation with inflammatory response process. Previous studies supported strong association between survival of transplanted stem cells and collective effects of reactive oxygen species and inflammatory response after stroke [65]. Hence, it can be inferred that the impact of inflammation-related mechanisms plays a significant role to determine the efficacy of stem cell transplantation as a therapeutic intervention for ischemic stroke. In the frontiers and hotspots analysis (Figure 9), "anti-inflammation", "inflammation", and "neuroinflammation" are popular keywords in recent years, reflecting that inflammation has become a significant focal point in this field. Despite the immunomodulatory role of stem cells and association with paracrine functions [66], the underlying mechanisms are not fully understood and worth to explore further.

Mesenchymal stem cells and ischemic stroke

In recent years, MSCs have received increased attention. Our findings suggest that 3 of top 10 co-cited references (Table 5) are related to clinical trials of MSCs. In keywords occurrences analysis (Figure 8), MSCs has a frequency of 263 times, and exhibits extensive links with other keywords, which is referred as a major focus in the field of stem cells and ischemic stroke. Furthermore, the analysis of keywords evolution trends in Figures 9 and Figures 10 depicts increased interest in recent times on MSCs. Additionally, MSCs have drawn a higher level of attention over the last 5 years as compared to NSCs. This suggests that MSCs may hold important possibilities in the application of ischemic stroke.

MSCs are present in various accessible donor tissues and possess the ability to differentiate into a diverse range of cell types, including neural cells [67, 68]. This characteristic provides MSCs a comparative edge over alternative stem cell types in research. Both *in vivo* and *in vitro* experiments have demonstrated that MSCs regulate the pathological processes of

ischemic stroke via multiple targets. Several studies showed that MSCs enhanced collateral circulation by upregulating proteins involved in collateral remodeling and rescued damaged neurons by mitochondrial transfer and immunomodulatory effect [69, 70]. MSCs are also known to facilitate axon regeneration via modulating the functioning of astrocytes and microglia [71].

Currently, there have been a total of 86 clinical trials conducted on the application of stem cells for ischemic stroke. Out of these trials, 31 of them specifically focus on the efficacy of MSCs, accounting for over one third of the total trials (*clinicaltrials.gov*, accessed Sep 15, 2023). The findings indicated that MSCs-based therapy is safe, feasible, and efficacious to treat patients with acute, subacute, and chronic ischemic stroke [72, 73]. Based on the available evidence, MSCs hold greater potential as a viable option for stem cells transplantation in the treatment of ischemic stroke.

However, the influence of MSCs' secretome on cellular functions varies significantly between MSC classes [74, 75]. In the absence of validated, secure, and reproducible cell extraction procedures, comparing the clinical outcomes of diverse clinical trials is difficult. Consequently, it is challenging to draw general conclusions regarding the effect of MSCs and secretome on ischemic stroke. Studies have shown that the origin, isolation, culture and amplification methods of stem cells significantly impacted the features and efficiency of MSCs [76-78]. In light of heterogeneity of MSCs and high complexity of local microenvironment, it is imperative to further explore the quality evaluation method of MSCs, which is a crucial step towards clinical translation.

Stem cells in angiogenesis after ischemic stroke

Our study suggests that angiogenesis is well recognised and prominent subject within the area. In top 10 high-cited articles (Table 4), two of them are related to the role of stem cells in angiogenesis after ischemic stroke. Ohab et.al defined a unique neurovascular niche in peri-infarct cortex, where angiogenesis and neurogenesis exhibit interdependence and mediated by specific vascular growth factors and chemokines [79]. Another study confirmed the crucial involvement of human cord blood derived CD34(+) cells in promoting the environment conducive for neovascularization of ischemic brain and enhancing neuronal regeneration [36]. Therefore, the presence of a favourable milieu that promotes angiogenesis is more conducive for nerve regeneration and functional recovery after ischemic stroke. The findings align with the outcomes reported

in a scholarly article based on the analysis of highly co-cited references [42] (refer to Table 5). As depicted in Figure 7, beside NSCs and MSCs, EPCs are the most commonly employed types of stem cells in ischemic stroke research. This observation indicates the important role of stem cell-induced angiogenesis on neural restoration following cerebral ischemia, while also offering substantiation for the safety and effectiveness of EPC transplantation. Moreover, as illustrated in Figure 8, the term "angiogenesis" exhibits the highest frequency of occurrence and occupies a central position inside cluster 6 (bright blue). Figure 8 also shows the strong association among "Nerve growth factor", "VEGF" and "angiogenesis", highlighting their crucial role in promoting neovascularization. The discovery of stem cells derived angiogenesis-related factors and the mechanisms of post-stroke angiogenesis will contribute to a comprehensive understanding of stem cell functions in ischemic stroke.

Extracellular vesicles and exosomes from stem cells in ischemic stroke

In top 20 references with strongest citation bursts (Table 6), Doeppner et al. suggests that MSCs derived EVs improved post-stroke neuroregeneration and brain remodeling, and provided valuable evidence to support the safety and efficacy of EVs in ischemic stroke [47]. Based on the temporal citation burst, it may be speculated that EVs have attracted great attention from research since 2018. A study in 2017 reported that transfecting miRNA into exosomes enhanced neuroplasticity and functional recovery following ischemic stroke [48]. This article had great citation burst from 2020 to 2022, reflecting the emergence of a novel topic in the field. Additionally, it was reported that #5 extracellular vesicles and #8 exosomes are latest main focus of research (Figure 6). Furthermore, Figure 9 indicates that AAY of EVs and exosomes is the most recent, which suggest that they are emerging as prominent areas of interest within this field. Therefore, EVs and exosomes may serve as a novel target for future research to evaluate the therapeutic potential in ischemic stroke.

A series of current studies have demonstrated that stem cell-derived exosomes play various roles in promoting neural repair after ischemic stroke, including inhibiting cell apoptosis and the inflammatory response, secreting angiogenesis factor, and stimulating axon regeneration and remodeling [80, 81]. As a cell-free therapy, EVs have significant clinical advantages over the latent tumorigenicity, low survival rate, and immune rejection of transplanted cells. However, there is no standard protocol for exosome collection, storage, transportation, or

delivery [82]. These unresolved issues can serve as prospective research attempts.

Advantages and limitations

We performed a comprehensive bibliometric analysis of publications in the field of stem cells and ischemic stroke and observed an increasing attention in this domain. First, the distribution and collaboration network of publications depicted the most influential countries and institutions. Encouraging profound cooperation among these prominent national institutions could enhance the advancement in this field. Second, analysis of keywords provides precise and deeper understanding of unique impacts of stem cells involved in the progression of ischemic stroke. It also identified several forefront topics of interest. Additionally, NSCs and MSCs are the most common types of stem cells utilised in clinical research. Safety, feasibility, and efficacy have been evaluated by previous clinical trials of ischemic stroke patients. Therefore, it is potentially promising option to further focus on stem cells with the aim of detailed investigation to ascertain effective therapeutic strategies for ischemic stroke.

However, it is irrefutable that our study has several limitations. Firstly, WoS database was only used to search relevant publications, whereas publications in other databases, such as PubMed and Scopus, may have been overlooked in our study, potentially introducing selection bias. Secondly, due to limited literature types and languages, our search strategy may not identify all the relevant references. Moreover, as the database is continuously updated, there is a discrepancy between the search results of this study and the actual number of articles included. However, we believe that comparable studies in the future will be able to resolve these limitations to the greatest extent.

Conclusions

Our bibliometric study depicted the global situation and research growth trends in the field of stem cells and ischemic stroke over the past 22 years. We showed that research on stem cells and ischemic stroke has received great attention in recent years, and the number of publications has increased steadily. We also identified the most influential country, institution, and journal in the field. Existing research focuses primarily on neurogenesis, inflammation, angiogenesis, EVs, MSCs and therapeutic efficiency of stem cells. However, there are still several unresolved issues with stem cell clinical translations. Topics related to miRNA, EVs, exosomes, MSCs, neuroinflammation and autophagy may represent future research frontiers. Our findings contribute to

identify research hotspots and trends, which provide novel opportunities for further study and application of stem cells in ischemic stroke.

Abbreviations

NPCs: neural precursor cells; SVZ: subventricular zone; MSCs: mesenchymal stem cells; EPCs: endothelial progenitor cells; VPCs: vascular progenitor cells; ESCs: embryonic stem cells; iPSCs: induced pluripotent stem cells; WoS: web of science; SCI-E: science citation index-expanded; SSCI: social sciences citation index; TP: total publications; TC: total citations; ACP: average citation per publication; SGZ: subgranular zone; NSCs: neural stem cells; OGD: oxygen glucose deprivation; MCAO: middle cerebral artery occlusion; EVs: extracellular vesicles; AAY: average appearing year; VEGF: vascular endothelial growth factor; Ang: angiotensin; PI3K: phosphatidylinositol 3-kinase; SDF-1 α : stromal cell-derived factor 1 α ; CXCR4: CXC chemokine receptor.

Supplementary Material

Supplementary tables.

<https://www.medsci.org/v21p0151s1.pdf>

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Author contributions

ZBD, XYL and CGM: conceptualization. TY and HXH: data collection and analysis. TY and JS: data standardization. TY and NJ: writing—original draft preparation. LJS, MMH, GK, HT, and CGM: writing—review and editing. XYL and ZBD: visualization. All authors contributed to the article and approved the submitted version.

Competing Interests

The authors have declared that no competing interest exists.

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