Exploring the landscape of stem cell research for Alzheimer's disease: A bibliometric analysis spanning 2002–2021

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Abstract: An increasing number of research on stem cells and Alzheimer's disease (AD) has been accomplished, making stem cells the research hotspot in the field. This study was conducted to identify the hotspots and trends of research related to stem cells and AD through a bibliometric analysis. A systematic search was performed in the Web of Science Core Collection database for relevant articles published from 2002 to 2021. Data were analyzed through Cite Space and VOS viewer. Stem cell research into AD covered 94 countries/regions, with a total of 3629 institutions participating, and showed an increasing trend every year, with the United States and China being the major countries studied. Takahashi's team cultured the induced pluripotent stem cells for the first time, which became the source of many researchers' theories. The University of California System is the organization with the most impact on research results. *Plos One* is the most popular journal. Maiese found that SIRT1 is the treatment target of AD, and his research results are the most. Research interests include brain, dentate gyrus, amyloid-beta, oxidative stress, neurodegeneration, inflammation, pluripotent stem cells, neutralistic stem cells, and microglia. Our study revealed the global research trend of stem cells in AD. At present, the research hotspot is the research of induced pluripotent stem cell models in AD. It provides important information and reference for researchers in this field.

Keywords: Stem cells; Alzheimer's disease; Bibliometrics; Research hotspots

CLC number: R963 **Document code:** A **Article ID:** 1003–1057(2023)10–813–22

1. Introduction

Alzheimer's disease (AD) is a neurodegenerative and progressive disease that gradually worsens[1–3]. It is considered to be age-related and usually with memory decline and cognitive impairment[4,5]. AD is the most common type of dementia. According to the 2018 World Alzheimer's Report, it is estimated that by 2030, approximately 82 million people will be affected by dementia worldwide[6,7]. AD will account for about 50%–60% of those affected patients[8]. It has become one of the leading causes of death. Various factors contribute to AD, such as aggregation of amyloid-beta, neuroinflammation, and neurofibrillary tangle formation[9–12]. Some drugs can slow the progression of AD, but no drugs are available that can provide a complete cure for AD at present. Thus, stem cell therapy turns up to be a novel approach to the treatment of AD[13–15]. Studies have shown promising results in the use of stem cells for the treatment of various clinically refractory diseases such as leukemia, Parkinson's disease, and AD[16–19]. Studies have shown that stem cells may have the potential to reduce the amounts of amyloid-beta and inflammation. Additionally, stem cells have the ability to differentiate into new

Received: 2023-04-18; Revised: 2023-05-09; Accepted: 2023-06-11.
Foundation items: Guangxi University of Traditional Chinese Medicine Postgraduate Education Innovation Project (Grant No. YCBXJ2022009); Guilin Science and Technology Bureau (Grant No. 2020011208-5); National Natural Science Foundation of China (Grant No. 81973768).
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http://dx.doi.org/10.5246/jcps.2023.10.066

neurons and activate endogenous stem cells[4,20,21]. Therefore, stem cell research is of great potential for the treatment of AD.

Bibliometric analyses have been previously conducted in breadth and depth in the field of neurological science but not yet specifically on stem cells in AD research[22–25]. Thus, we sought to gain a comprehensive and detailed view of the research related to stem cells and AD over the last two decades through bibliometric analysis, using Cite Space 6.1.R3 and Vos viewer 1.6.18. By analyzing authors, countries, institutions, keywords, and references, the study aimed to identify knowledge structure, research trends, and hotspots in this field[26,27].

2. Materials and methods

2.1. Data source and search strategy

To ensure the accuracy of the literature search, we used the Medical Subject Headings (Mesh) terms and retrieved and downloaded data from the Web of Science Core Collection database (WoSCC) on a specific date (October 3, 2022) to reduce potential bias caused by database updates. The search strategy was as follows: (TS = (Stem Cells or Mother Cells or Colony Forming Units or Progenitor Cells) and TS = (Alzheimer Disease or Alzheimers Diseases or Alzheimer Dementia or Alzheimer Syndrome or Alzheimer Sclerosis or Senile Dementia or Presenile Dementia). A total of 4890 documents were retrieved from 01/01/2002 to 12/31/2021. Documents in a non-English language, abstracts, editorial materials, book chapters, conference proceedings papers, revisions, letters, news, online publications, and retracted articles were excluded. Duplicate articles were checked by Cite Space, and if repeated documents were found, a double check would be done by reading their titles, abstracts, authors, and keywords. Only articles and reviews are selected to be analyzed. Finally, a total of 4627 publications were included, of which 3067 were articles, accounting for 66.29% of the total publications, and 1560 were reviews. Literature inclusion was done through steps in Figure 1.

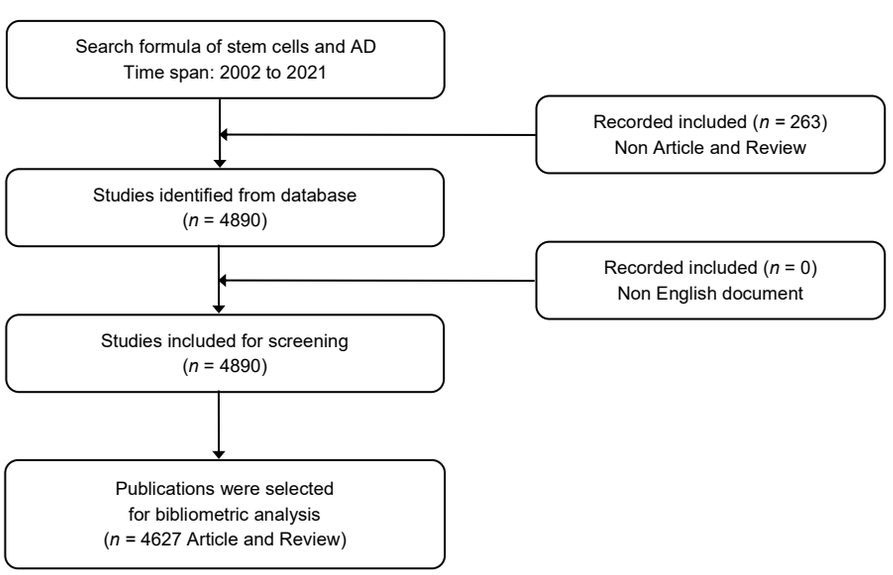

Figure 1. Flow chart of literature inclusion.

2.2. Bibliometric analysis

All the retrieved documents were exported as "Full Record and Cited References" in the format of "Plain text file" and saved as "download_xxx.txt" format. For the settings in Cite Space software: we set the time span from 2002 JAN to 2021 DEC, Years Per Slice: 2. For the settings in Node Types, the following "Author, Institution, Country, Keyword, Reference, Cited Author, Cited Journal" were selected, and the rest of the software settings remained unchanged. For the settings in VOS viewer software, the minimum co-occurrence thresholds were set to be 12 for authors, 40 for institutions, and 60 for countries/regions. The minimum citation thresholds were set to be 120 for authors, 2600 for institutions, and 200 for countries/regions. The minimum keyword emergence threshold was set to 180. In the VOS viewer graph, the nodes represent the objects of analysis, with their size indicating their frequency of occurrence (or citation frequency). The thickness of the lines between nodes represents the strength of the co-citation relationship[28–32]. H-index evaluates the academic impact of authors or countries/regions, institutions, and journals[23,30,33].

3. Results

3.1. Publication trends

We obtained a total of 4627 articles on research related to stem cells and AD in the Web of Science database. Figure 2 shows an upward trend in the number of articles published on stem cell research related to AD from 2002 to 2021, with some fluctuations in the number of articles in 2007 and 2009. The fewest articles were published in 2002 (n = 36, 0.78%), while the most prolific year in terms of publications was 2021 (n = 517, 11.17%). Figure 3 shows the publishing trend of the top 10 countries: China has published relevant articles since 2004. The growth of publications was the fastest in the United States and China.

3.2. Analysis of countries/regions and institutions

The 4627 publications were from 94 countries/regions. The top three countries (Table 1) in terms of publications on stem cell research related to AD were the United States (n = 1689, 36.50%), China (n = 788, 17.03%), and Germany (n = 348, 7.52%). The United States appeared to be the leader in terms of total publications, total citations (n = 109 791), H-index (n = 153), and total link strength (n = 746), with a particularly strong network of connections with other countries, including China, Germany, and the United Kingdom (Fig. 4). Germany had the highest average citations per article (n = 84.95). Both the United States and China had the largest area, but most connections were emanating from the United States (Fig. 5).

In the past two decades, 3629 institutions issued publications on research related to stem cells and AD. The top three institutions (Table 2) with at least 100 publications were the University of California System (n = 325, 14.24%), Harvard University (n = 262, 5.66%), and the University of London (n = 133, 2.88%). The University of California System had the most publications and highest H-index (n = 71), while the National Institutes of Health had the highest average citations per article (n = 90.46).

3.3. Analysis of journals

Articles related to stem cells and AD were published in 993 academic journals. The top three journals (Table 3) in terms of the number of publications were *Plos One* (n = 121, 2.62%), *International Journal of Molecular Sciences* (n = 111, 2.40%), and *Journal of Alzheimer's Disease* (n = 95, 2.05%). *Plos One* was the journal with

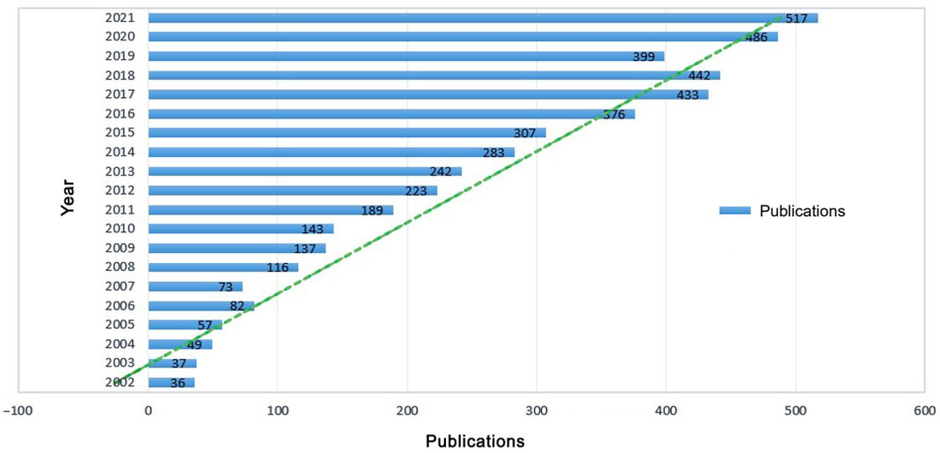

Figure 2. Global trend of publications related to stem cells and AD from 2002 to 2021.

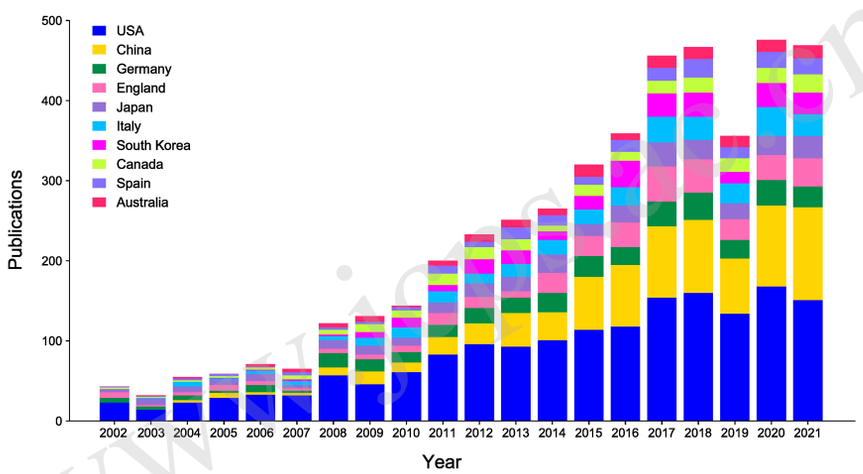

Figure 3. Annual publications of the top 10 countries on research related to stem cells and AD from 2002 to 2021.

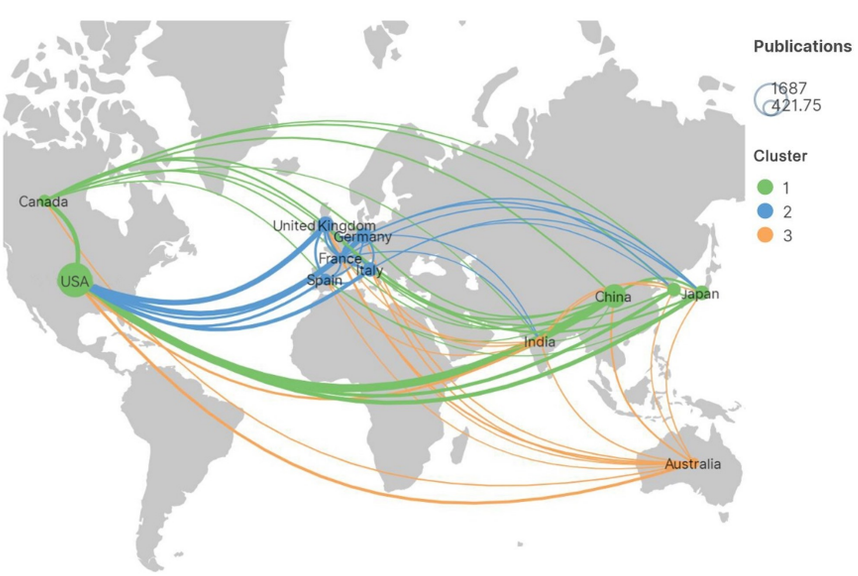

Figure 4. The geographical distribution of cooperation between countries/regions related to stem cells and AD.

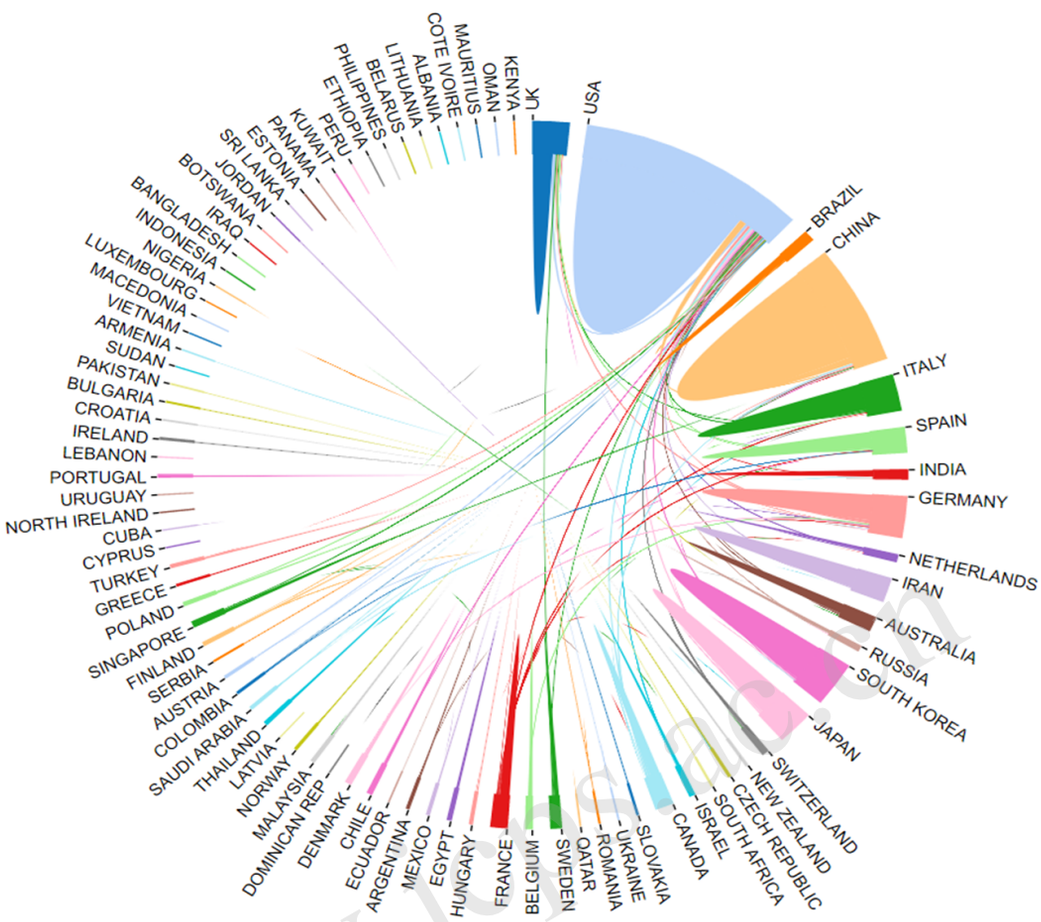

Figure 5. The knowledge map of countries/regions' cooperation related to stem cells and AD.

Table 1. Top 10 countries/regions publications related to stem cells and AD.

Rank	Country/region	Counts	Percentage	Total citations	Average citation per item	H-index	Total link strength
1	USA	1689	36.50	109 791	65.00	153	746
2	China	788	17.03	18 278	23.20	62	247
3	Germany	348	7.52	29 563	84.95	76	305
4	England	343	7.41	18 861	54.99	70	358
5	Japan	303	6.55	13 748	45.37	64	173
6	Italy	296	6.40	11 758	39.72	55	188
7	South Korea	260	5.62	9398	36.15	52	102
8	Canada	209	4.52	11 889	56.89	62	191
9	Spain	185	4.00	10 300	55.68	48	135
10	Austria	154	3.33	8431	54.75	47	108

Table 2. Top 10 institutions in the number of published articles related to stem cells and AD.

Rank	Institution	Counts	Percentage	Average citation per item	H-index	Country/region
1	University of California System	325	14.24	90.13	71	USA
2	Harvard University	262	5.66	65.51	57	USA
3	University of London	133	2.88	50.98	43	England
4	National Institutes of Health	98	2.12	91.46	42	USA
5	UDICE French Research Universities	91	2.00	68.98	38	France
6	University College London	88	1.90	50.81	36	England
7	Helmholtz Association	82	1.77	62.17	37	USA
8	State University of Florida	82	1.77	38.74	28	USA
9	Chinese Academy of Sciences	76	1.63	39.63	30	China
10	Johns Hopkins University	72	1.55	84.65	37	USA

the most published articles. *Journal of Neuroscience* had the highest H index (*n* = 41) and IF (*n* = 6.709), while *Neurobiology of Aging* had the highest average citations per article (*n* = 160.41).

Journal co-citations show the interrelationships between journals and disciplines[34]. Table 4 shows that the *Journal of Neuroscience* (*n* = 667 837) had the most co-citations, followed by *Proceedings of the National Academy of Sciences of the United States of America* (*n* = 622 766) and *Nature* (*n* = 595 768). *Journal of Neuroscience* had the highest total link strength and H-index (*n* = 41), while *Nature* had the highest IF (*n* = 69.504), and *Science* had the highest average citations per article (*n* = 931.20). Figure 6 indicates that the above-mentioned four journals had the largest nodes and the densest connection lines. The cross-citation of academic journals, as indicated by the orange paths (Fig. 7), revealed that papers published in molecular, biological, and immunological journals were mainly cited by papers within these journals. Cross-citation of academic journals helps enhance academic communication, but it is still the top journals that lead academic advancement.

3.4. Analysis of authors

A total of 22 718 authors in total were involved in the studies related to stem cells and AD. Among the top 10 productive authors (Table 5), Maiese published the most papers (*n* = 26, 0.56%), followed by Okano (*n* = 20, 0.43%) and Chang (*n* = 19, 0.41%). Maiese also had the highest H-index (*n* = 22). Gage had the highest average citations per article (*n* = 452.56). The time overlay map of the author's collaboration network (Fig. 8) showed a lack of close interaction among the authors.

The analysis of the co-citation of authors in their publications reveals the research groups or collaborations that are considered most influential in the field[34,35]. Table 6 suggests that Takahashi (*n* = 802), Maiese (*n* = 752), and Selkoe (*n* = 674, total link strength = 3086, H-index = 6) were the top three frequently cited authors in the field. Takahashi from Japan had the highest citation frequency. Maiese ranked first in total link strength (*n* = 10 770), while Chong ranked 2nd (*n* = 10 770). The authors' co-citation networks are shown in Figure 9. Maiese and Chong had the thickest interconnections, indicating that they were the most co-cited among all authors in the field.

3.5. Analysis of reference

The paper by Israel et al. in *Nature* in 2012 (*n* = 358) was the most co-cited paper, followed by the two papers by Takahashi et al. in *Cell* in 2007 (*n* = 351) and 2006 (*n* = 336) (Table 7). The articles with the highest H index (*n* = 1 069) were published by Dimos in 2008, Israel in 2012, and Choi in 2014. The largest nodes and the densest connections were found for authors Israel and Takahashi (Fig. 10).

Figure 11 displays 25 references with the strongest citation bursts. The first paper with a burst was published in the *Journal of Neurochemistry* in 2002 by Haughey et al. with a focus on the pathological mechanism of neural progenitor cells on AD. The reference with the highest burst strength (*n* = 38.71) was published by Jin et al. in 2004 in *Proceedings of the National Academy of Sciences of the United States of America*[36] on neuropathy in the hippocampal region of AD patients. The burst strength of the top 25 references in terms of citation frequency ranged from 23.37 to 38.71 and burst duration ranged from 3 to 8 years. Moreover, 11 of the co-cited references had burst up to the present, indicating that they were current subjects of research and should be addressed in detail in the discussion section.

Table 3. Top 10 productive journals related to stem cells and AD.

Rank	Journal	Counts	Percentage	Average citation per item	H- index	IF (2021)	Quartile in category
1	*PLoS One*	121	2.62	41.12	39	3.752	Q2
2	*Int J Mol Sci*	111	2.40	26.71	33	6.208	Q1
3	*J Alzheimers Dis*	95	2.05	24.69	29	4.160	Q1
4	*Mol Neurobiol*	82	1.77	25.87	28	5.682	Q1
5	*Sci Rep*	81	1.75	31.10	27	4.996	Q2
6	*J Neurosci*	63	1.36	93.25	41	6.709	Q1
7	*Front Cell Neurosci*	62	1.34	33.44	23	6.147	Q1
8	*Stem Cell Res*	57	1.23	10.81	12	1.587	Q4
9	*Neural Regen Res*	54	1.17	16.50	17	6.508	Q2
10	*Neurobiol Aging*	54	1.17	160.41	31	5.133	Q2

Table 4. Top 10 co-cited journals in terms of citation frequency related to stem cells and AD.

Rank	Co-cited Journal	Total link strength	Citation frequency	Average citation per item	H-index	IF (2021)	Quartile in category
1	*J Neurosci*	667 837	13 912	93.25	41	6.709	Q1
2	*P Natl Acad Sci USA*	622 766	13 542	155.29	21	12.779	Q1
3	*Nature*	595 768	12 937	453.10	10	69.504	Q1
4	*Science*	463 156	9172	931.20	5	63.714	Q1
5	*J Biol Chem*	367 404	8418	72.84	24	5.486	Q2
6	*Cells*	368 009	7745	16.83	14	7.666	Q2
7	*Plos One*	311 374	7219	41.12	39	3.752	Q2
8	*Neuron*	349 167	6965	215.95	18	18.688	Q1
9	*Cell Stem Cell*	266 879	5227	215.73	21	25.269	Q1
10	*J Neurochem*	263 450	5207	67.67	27	5.564	Q2

Table 5. Top 10 productive authors in research related to stem cells and AD.

Rank	Author	Counts	Percentage	Average citation per item	H-index	Country/region
1	Maiese, K.	26	0.56	62.83	22	USA
2	Okano, H.	20	0.43	97.92	12	Japan
3	Chang, J.W.	19	0.41	32.30	13	South Korea
4	Na, D.L.	18	0.39	15.42	11	South Korea
4	Blurton-jones, M.	18	0.39	108.00	14	USA
6	Mattson, M.	17	0.37	202.09	11	USA
6	Rivest, S.	17	0.37	107.60	16	Canada
8	Gage, F.H.	16	0.35	452.56	17	USA
8	Goldstein, L.S.B.	16	0.35	95.65	13	USA
8	Lazarov, O.	16	0.35	123.40	10	USA
8	Tsai, L.H.	16	0.35	97.19	11	USA

Table 6. Top 10 co-cited authors in research related to stem cells and AD.

Rank	Co-cited Author	Citation frequency	Total link strength	H-index	Country/region
1	Takahashi, K.	802	4224	6	Japan
2	Maiese, K.	752	10 770	22	USA
3	Selkoe, D.J.	647	3086	6	USA
4	Jin, K.L.	608	4149	3	USA
5	Kempermann, G.	568	4609	9	Germany
6	Braak, H.	471	2006	5	Germany
7	Mattson, M.P.	470	2151	25	USA
8	Chong, Z.Z.	424	10 096	11	USA
9	Hardy, J.	404	2198	12	England
10	Van, Praag, H.	386	3267	3	USA

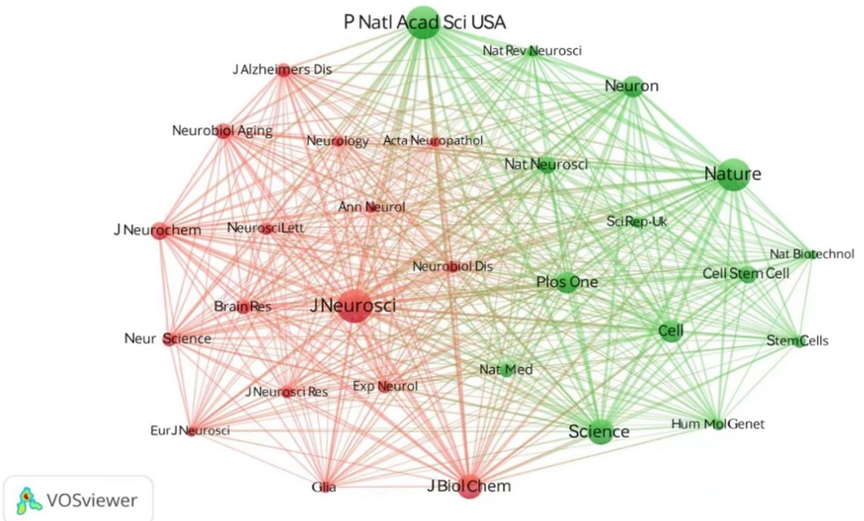

Figure 6. Knowledge map of co-cited reference network for research related to stem cells and AD.

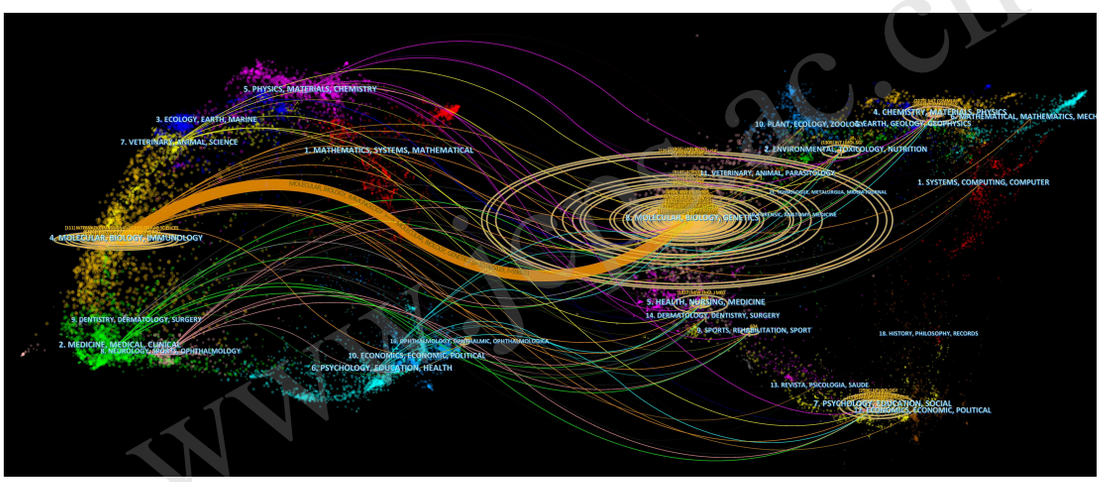

Figure 7. Biplot overlay of journal citations for research related to stem cells and AD.

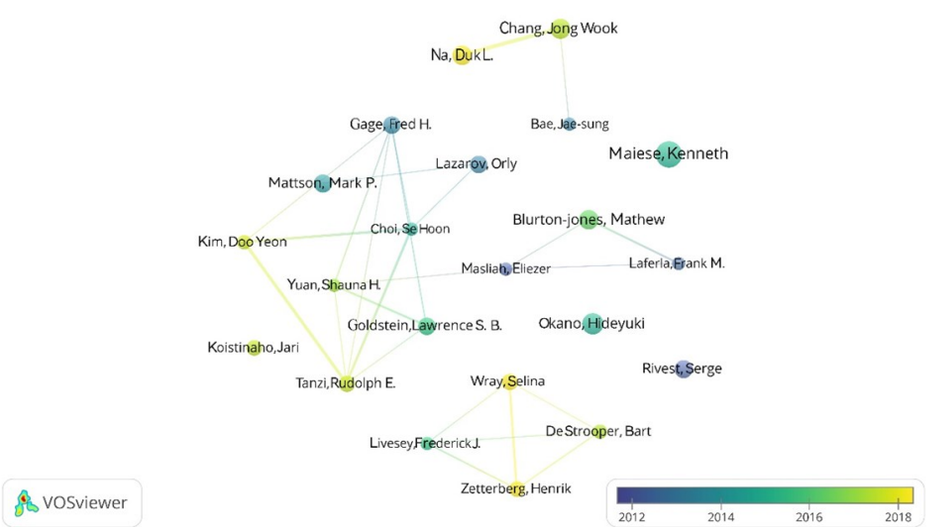

Figure 8. Time overlay map of author's collaboration network for research related to stem cells and AD.

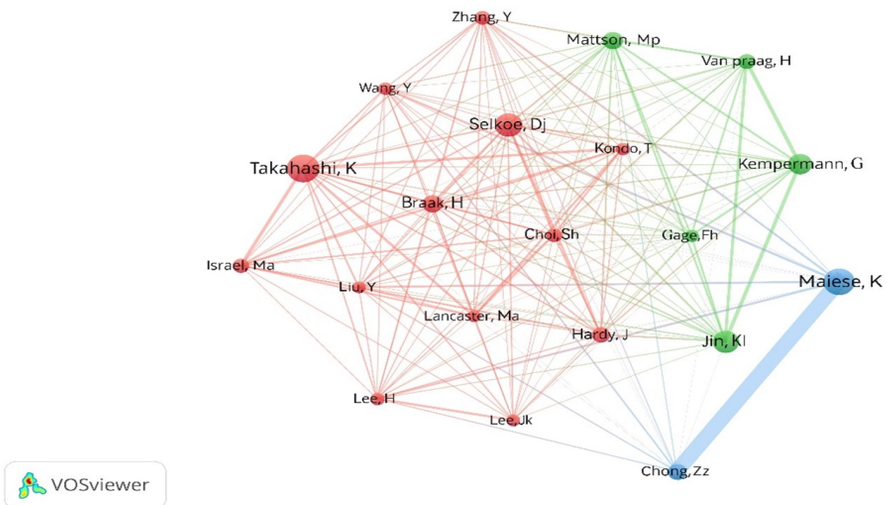

Figure 9. Author's co-citation network in research related to stem cells and AD.

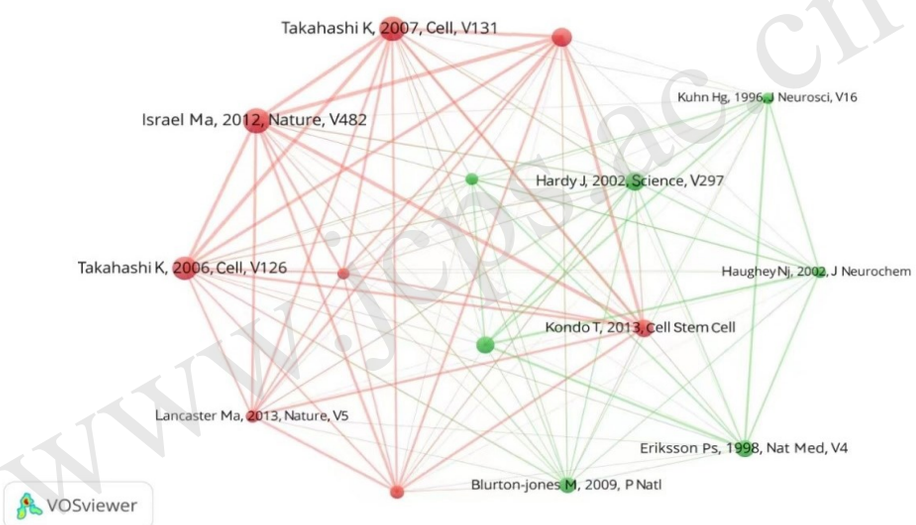

Figure 10. Map of co-cited reference network on research related to stem cells and AD.

Table 7. Top 10 co-cited references on research related to stem cells and AD.

Rank	Co-cited reference	Author and publication year	Citations	Total link strength	Journal IF (2021)	H-index	Quartile in category
1	Probing sporadic and familial Alzheimer's disease using induced pluripotent stem cells	Israel, M.A., 2012	358	1650	*Nature* (IF: 69.504)	1069	Q1
2	Induction of pluripotent stem cells from adult human fibroblasts by defined factors	Takahashi, K., 2007	351	1525	*Cell* (IF: 66.850)	705	Q1
3	Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors	Takahashi, K., 2006	336	1279	*Cell* (IF: 66.850)	705	Q1
4	Modeling familial Alzheimer's disease with induced pluripotent stem cells	Yagi, T., 2011	267	1419	*Hum Mol Genet* (IF: 5.121)	255	Q1
5	The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics	Hardy, J.L, 2002	258	559	*Science* (IF: 63.714)	1058	Q1
6	Modeling Alzheimer's disease with iPSCs reveals stress phenotypes associated with intracellular Aβ and differential drug responsiveness	Kondo, T., 2013	250	1197	*Cell Stem Cell* (IF: 25.269)	212	Q1
7	Increased hippocampal neurogenesis in Alzheimer's disease	Jin, K.L., 2004	242	608	*P Natl Acad Sci USA* (IF: 12.779)	699	Q1
8	Neural stem cells improve cognition *via* BDNF in a transgenic model of Alzheimer disease	Blurton-Jones, M., 2009	219	336	*P Natl Acad Sci USA* (IF: 12.779)	699	Q1
9	A three-dimensional human neural cell culture model of Alzheimer's disease	Choi, S.H., 2014	184	716	*Nature* (IF: 69.504)	1069	Q1
10	Cerebral organoids model human brain development and microcephaly	Dimos, J.T., 2008	176	776	*Nature* (IF: 69.504)	1069	Q1

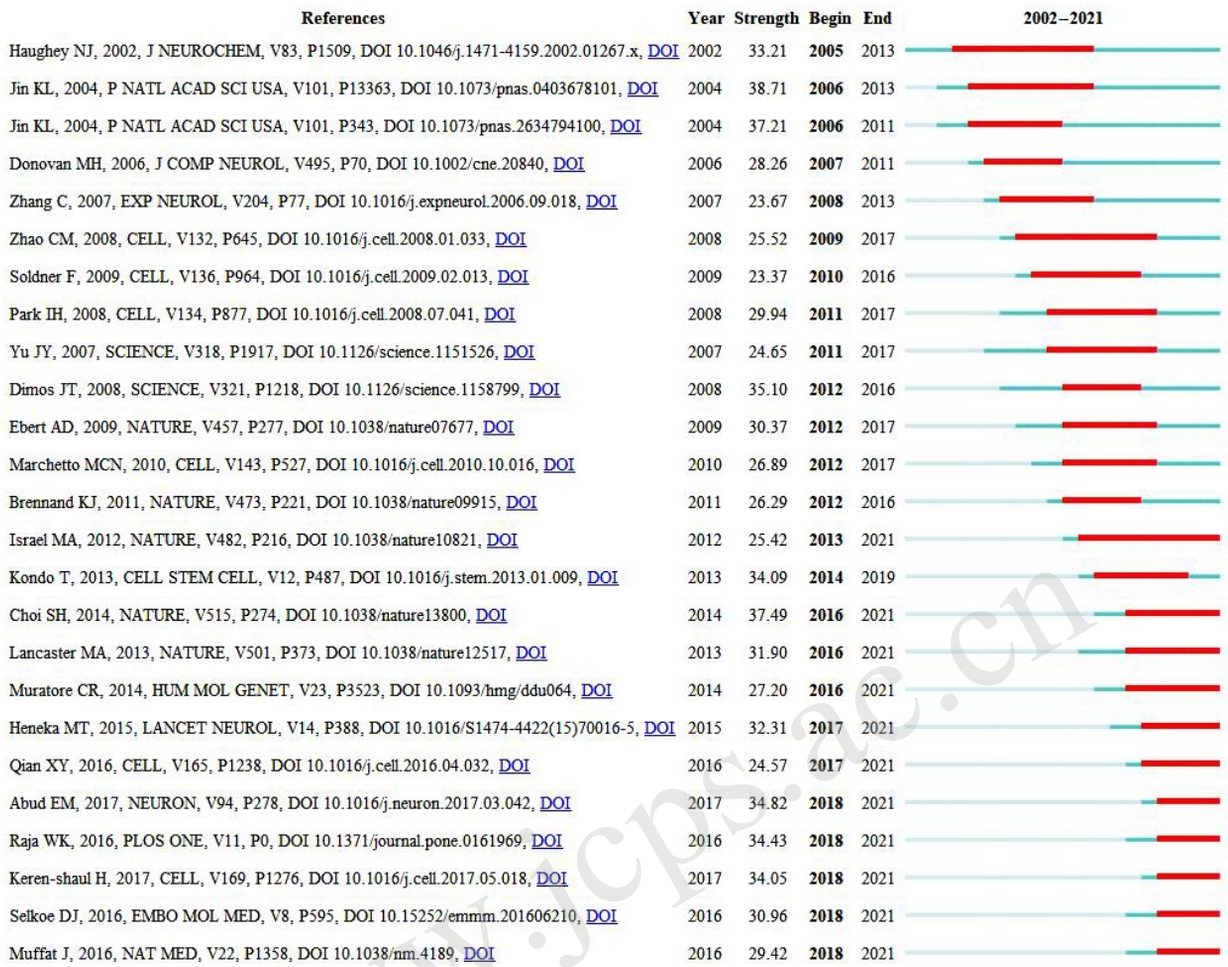

Figure 11. Top 25 references with the strongest citation bursts.

3.6. Analysis of keywords

Keywords that occurred at least 180 times were enlisted and ranked in Table 8, of which the top three were: AD (n = 3247), brain (n = 2535), and stem cells (n = 510). AD was the keyword with the highest frequency of occurrence and total link strength. The time overlay map of the keyword co-occurrence network (Fig. 12) revealed different clusters of keywords. Keywords in color yellow were mainly pluripotent stem cells, amyloid-beta, protein, transplantation, inflammation, microglia, etc., while keywords in purple were mainly dentate gyrus, proliferation, hippocampal neurogenesis, progenitor cells, etc.

The keywords (Fig. 13) with the earliest burst were rat brain (n = 2002), dentate gyrus (n = 2002), and precursor protein (n = 2002), while the keywords with the longest burst duration were neural progenitor cell (n = 10), subventricular zone (n = 10), and dopaminergic neuron (n = 10). The keywords that burst to the present were mechanism (n = 2021), cognitive impairment (n = 2021), microglia (n = 2021), cerebrospinal fluid (n = 2021), and gene (n = 2021).

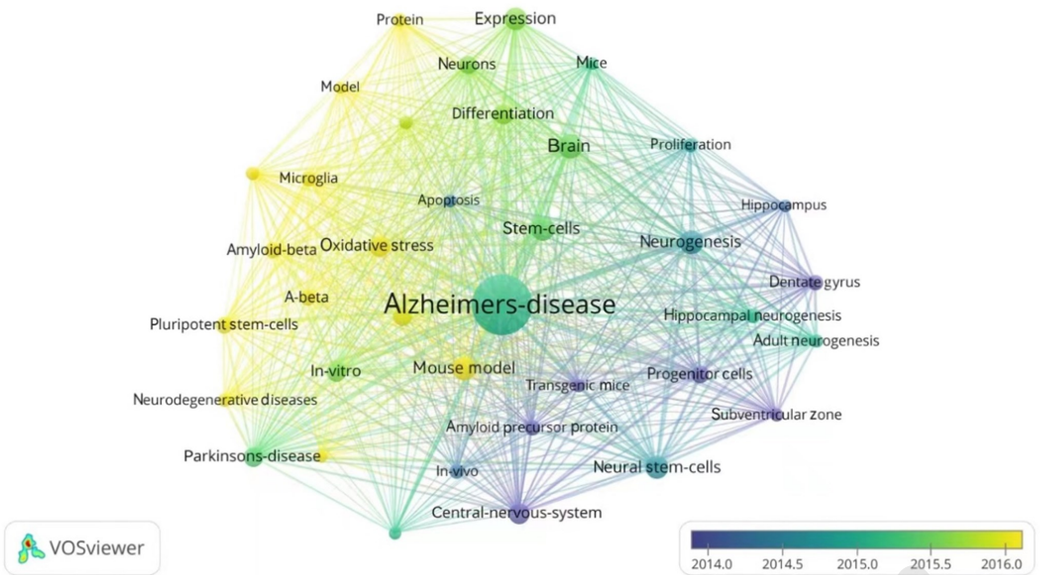

Figure 12. The time overlay map of keyword co-occurrence network on research related to stem cells and AD.

Keywords	Year	Strength	Begin	End	2002–2021
Rat brain	2002	13.28	2002	2010	
Dentate gyrus	2002	10.24	2002	2010	
Precursor protein	2002	8.16	2002	2010	
Neural progenitor cell	2002	22.83	2003	2013	
Subventricular zone	2002	20.66	2003	2013	
Central nervous system	2002	14.31	2003	2008	
Dopaminergic neuron	2002	15.55	2004	2014	
Peptide	2002	8.72	2004	2013	
Spinal cord	2002	8.49	2004	2010	
Long term potentiation	2002	15.79	2005	2014	
Growth factor	2002	14.55	2005	2011	
Nervous system	2002	12.40	2005	2012	
Focal cerebral ischemia	2002	10.96	2005	2011	
Neurite outgrowth	2002	8.21	2005	2014	
Embryonic stem cell	2002	15.10	2008	2015	
Spinal cord injury	2002	12.15	2008	2012	
Adult hippocampal neurogenesis	2002	17.69	2010	2016	
Familial alzheimers disease	2002	17.17	2012	2017	
Generation	2002	17.03	2012	2016	
Human fibroblast	2002	12.59	2012	2014	
Motor neuron	2002	11.93	2012	2015	
Nerve growth factor	2002	11.87	2013	2015	
Traumatic brain injury	2002	15.38	2014	2017	
Directed differentiation	2002	10.63	2015	2017	
Alzheimer disease	2002	10.58	2016	2019	
Mechanism	2002	10.62	2017	2021	
Cognitive impairment	2002	20.32	2018	2021	
Microglia	2002	17.71	2018	2021	
Cerebrospinal fluid	2002	12.67	2018	2021	
Gene	2002	8.84	2018	2021	

Figure 13. Top 30 keywords with the strongest citation bursts.

Table 8. Top 30 high-frequency keywords in research related to stem cells and AD.

Rank	Keyword	Frequency	Total link strength	Rank	Keyword	Frequency	Total link strength
1	AD	3247	5950	16	Pluripotent stem-cells	301	778
2	Brain	2535	1954	17	Amyloid-beta	282	282
3	Stem cells	510	1582	18	Microglia	269	1022
4	Mouse model	509	1896	19	Dentate gyrus	264	1236
5	Neurogenesis	508	2177	20	Amyotrophic lateral sclerosis	262	823
6	Neural stem cells	494	1858	21	*In-vivo*	243	796
7	Expression	460	1.394	22	Hippocampal neurogenesis	242	1126
8	Oxidative stress	427	1.350	23	Proliferation	237	1029
9	Central-nervous-system	424	1537	24	Protein	223	748
10	Differentiation	400	1397	25	Transgenic mice	221	873
11	Parkinson's Disease	389	1276	26	Adult neurogenesis	218	1.061
12	*In-vitro*	381	1161	27	Subventricular zone	215	997
13	Neurodegeneration	356	1260	28	Inflammation	214	765
14	Neurons	342	1206	29	Transplantation	212	739
15	Progenitor cells	316	1252	30	Mice	206	766

4. Discussion

4.1. General information

A total of 4627 articles in the WoSCC database were found to have related to stem cells and AD, by 22 718 authors from 3629 institutions in 94 countries/regions. Figure 2 shows that the number of publications was increased by about 14 times over the past 20 years (2002 to 2021). This period was roughly divided into three developmental phases: 2002 to 2007 was the start-up phase of research. The average number of publications per year was approximately 56, and the year 2006 had the highest number of publications (n = 82, 1.77%). From 2012 to 2021, the research witnessed rapid development. The average annual number of publications reached 371. In particular, the number of publications in 2021 exceeded 500 and accounted for 11.17% of the total volume of publications. However, there was a decrease of 43 publications from 2018 to 2019, going from 442 in 2018 to 399 in 2019. This may be due to various factors, including the global outbreak of COVID-19, which has had a significant negative impact on both the global economy and scientific research[37,38]. The increasing number of researchers worldwide engaging in research related to stem cells and AD indicates a promising future for such research.

The United States was a major contributor to the research related to stem cells and AD. It cooperated most closely with China, followed by Germany and the UK (Fig. 4). The US and the UK cooperated most extensively with other countries (Fig. 5). The United States and China were the top two countries that contributed the most to publications worldwide in the field of AD, accounting for more than 50% of the total publication volume. China was the only developing country that got ranked in the top 10 countries. Although it was the second most productive country, it had the lowest average citation frequency per article, indicating a need to improve the quality of its research. Germany published only 348 articles but had the highest average citation frequency per article, indicating a high-quality research output. The top 10 institutions were mainly from the United States (60%), England (20%), Germany (10%), and China (10%). The US and European institutions contributed the most, and Asian countries need to work on improving their research capabilities.

Many articles (1161) were published in the top 10 journals in the field of stem cells and AD, accounting for 25.09% of all articles published. Moreover, 50% of those journals belonged to Q1, and 40% belonged to Q2 in the Scientific Citation Index division. *Plos One* was the most popular go-to choose for publishing research results in this field. *Journal of Neuroscience* was highly cited in the relevant research field, showing its high impact. *Neurobiology of Aging* was the journal with the highest average citation frequency despite publishing the smallest number of articles. It may attribute to its publication of only high-impact articles. The fact that the top 10 co-cited journals in the field of stem cells and AD were ranked in Q1 or Q2 indicated that high-quality journals tended to be more frequently cited than lower-quality journals. *Nature* and *Scienc*e had the highest IF and average citation per paper, respectively. These international authoritative journals provided strong support to research related to stem cells and AD.

The top 10 highly productive authors were mainly from North America and Asia, among which 7 out of 10 were from the United States. They published a total of 199 research results, accounting for 4.30% of the total literature. Maiese and Gage from the United States were the most prolific authors, with the highest H-index and average citation per article. Their high-quality research has earned a high academic reputation in the field, and their work has been widely cited by researchers. Maiese's research on SIRT1 as an effective target for the treatment of AD[39–41], and Gage's investigation of pathological mechanisms of AD through stem cell proliferation and differentiation[42–45] have both been particularly impactful. In the time overlay map of the author collaboration network (Fig. 8), the sparse connection between authors indicated low levels of collaboration, suggesting the need for closer academic communication to promote research progress in future studies. The top 10 co-cited authors in the field of stem cells and AD were all from developed countries, particularly in North America and Europe, with the United States and Japan leading the way. In addition, 60% of authors were from the U.S. Takahashi from Japan had the highest Citation frequency. Maiese and Chong had the closest cooperation with each other and collaborated most extensively with other investigators (Fig. 9).

4.2. Basic knowledge

The co-citation analysis of the literature allows us to identify the literature with academic impact and explore the research trends in the field[46,47]. The top 10 highly cited papers are all in Q1 journals, and 60% of them are published in the top journals *Nature*, *Cell*, and *Science*. Besides, 9 out of 10 papers were basic research, and one was a review. This finding indicated that these high-quality papers laid the theoretical foundation for the research field. These 10 papers were broadly divided into three research directions.

The first direction focused on the pathological mechanism of AD. Hardy et al. published an article in 2002 on AD in *Science.* This article provided valuable insights into the underlying cause and potential treatments for AD, the imbalance of amyloid-beta production and clearance[48]. The study by Jin et al. in *Proceedings of the National Academy of Sciences of the United States of America* in 2004 suggested that the lost neurons in AD patients were related to neural regeneration in the hippocampus, and enhancing hippocampal neurogenesis could be a new strategy for treating AD[36].

The second direction covers important studies on stem cells in various fields. Although these studies were not directly related to AD, they indirectly promoted the progress of the later research into stem cells for AD. Takahashi's team published important findings in *Cell* in 2006 and 2007, respectively. They confirmed that iPSCs could be generated from mouse embryonic or fibroblast

cells through Oct3/4, Sox2, Klf4, and c-Myc[49,50]. In 2013 in *Nature*., Lancaster et al. showed their result in developing a human pluripotent stem cell-derived three-dimensional organoid culture system that could recapitulate development and disease[51].

The third direction is to explore the use of stem cells, particularly for AD. In 2009, Blurton-Jones et al. published a research result in *Proceedings of the National Academy of Sciences of the United States of America* that neural stem cells could improve the clinical symptoms of AD through brain-derived neurotrophic factors[52]. In 2011, Yagi et al. published a paper in *Human molecular genetics*, which found that the FAD-iPSC-derived neuron was a valid model of AD and would provide an innovative strategy for the study of AD[53]. They provided a new strategy for AD research. In 2012, Israel's team published in *Nature* the result of research that the use of induced pluripotent stem cells could identify phenotypes relevant to AD at an early stage[54]. In 2013, Kondo's team published a paper in *Cell Stem Cell.* They simulated familial and sporadic AD disease models through iPSCs, and these models were able to analyze AD pathogenesis and evaluate drugs. In 2014, Choi's research team published an important paper in *Nature.* They used neural stem cells to create a three-dimensional neural cell model culture system. The system has the function of recapitulating the amyloid-beta and tau pathology of AD. This model served as an accurate human cell model for studying AD[55].

In general, by analyzing these 10 papers, stem cells, hippocampal neurogenesis, neurons, pluripotent stem cells, models, amyloid-beta, dentate gyrus, neural stem cells, etc. were the main research topics of the research related to stem cells and AD.

4.3. Hotspots and trend analysis

By analyzing the keyword co-occurrence, keyword bursts, and literature bursts, the research trends and hot spots of stem cell studies on AD will be detected[25,56–58]. The top 30 keywords of high frequency shown in the table were roughly divided into four categories (Table 8): (A) studies of AD lesion sites (e.g. brain, dentate gyrus, subventricular zone, and hippocampal neurogenesis); (B) studies on the pathological mechanism of AD (e.g. amyloid-beta, neurogenesis, oxidative stress, neurodegeneration, and inflammation); (C) studies of the types and characteristics of stem cells (e.g. some of the key types like pluripotent stem cells, neural stem cells, progenitor cells, microglia, proliferation, and key characteristics like differentiation); and (D) studies on animal models and intervention methods (e.g. mouse model, transgenic mice, *in-vitro*, *in-vivo*, and transplantation). These four categories of keywords revealed the focus of the studies related to stem cells and AD. The approximate time course of the research related to stem cells and AD can be identified from Figures 12 and 13. The purple keywords and the keywords with the earliest burst time were the main early research subjects, such as the keyword "dentate gyrus". Yellow keywords are those with the longest bursts time. They were often the subjects of current studies and known as research hotspots, such as the keyword "microglia". A keyword with the longest burst time may suggest that this term has been a subject of sustained research interest in this field, such as the keyword "neural progenitor cell". The literature burst shows the emerging research subjects and research hotspots in the field[59,60]. As in Figure 11, 11 of the references had bursts up to the present, which reflected the latest research trends in this study. Such trends have therefore been discussed further. Choi et al. (2014) published a paper in *Nature* with the highest burst strength (Strength = 37.49), and it was also one of the top 10 co-cited papers. The study used a three-dimensional neural cell model culture system derived from neural stem cells to recapitulate the pathological characteristics of amyloid β and tau in

AD patients. This system provided an accurate human cell model for the study of AD. Abud et al. (2017) published in *Neuron* a paper with the second highest burst strength (Strength = 34.82) which focused on microglial-like cells (iMGLs) differentiated from human iPSCs to study the function of microglial cells. The third highest burst strength study by Raja et al. in *Plos One* (Strength = 34.43) in 2006 found that a three-dimensional brain organ culture system could be derived from iPSCs[61] and used to investigate the effects of β- and γ-secretase inhibitors on reducing amyloid. Such a model can be used for drug discovery in AD. Keren-Shaul et al. (2017) published a paper in *Cell* with the fourth highest burst strength (Strength = 34.05) that novel microglia were found through examinations of its markers, spatial localization, and pathways of action. As novel microglia could limit AD lesions, it could be a new targeted agent for the treatment of AD[62]. Heneka et al. (2015) published in *Lancet Neurology* a paper with the fifth highest burst strength (Strength = 32.31), showing that internal and external inflammatory factors were causative factors of AD, and modulation of immune mechanisms was an approach to treat and prevent AD[63]. In 2013, Lancaster et al. published important findings in *Nature* (Strength = 31.90). They developed a human pluripotent stem cell-derived three-dimensional organoid culture system which can recapitulate development and disease. They also modeled microcephaly. Microcephaly is found to be caused by premature neuronal differentiation in the brain[51]. In 2016, Selkoe et al. Published a paper in *EMBO Molecular Medicine* (Strength = 30.96). The study confirmed that the cause of AD was the imbalance between the production and clearance of amyloid β-protein, and regulating the imbalance was the key for treatment[64]. In 2016, Muffat et al. published a study in *Nature Medicine* (Strength = 29.42). This study was the first to rapidly derive microglia from human pluripotent stem cells[65]. In 2014, Muratore et al. published a paper in *Human molecular genetics* (Strength = 27.20), which showed that a model of familial AD constructed by using iPSCs-derived neuronal cultures[66] was the most efficient model to study the process of the disease. In 2012, Israel et al. published important findings in *Nature* (Strength = 25.42). They found that observation of the AD phenotype using iPSCs could distinguish sporadic or familial AD in the early phase of AD[54]. In 2016, Qian et al. published an important paper in *Cell* (Strength = 24.57). The study found the use of human iPSCs to derive a Miniaturized Bioreactor Spinner, a modeling apparatus that could modulate human brain development, disease, and compound testing[67]. Through the above analysis, we found that induced pluripotent stem cells have emerged as a powerful tool for modeling AD, such as 2D, cerebellar organoids, hippocampal organoid models, and especially the whole brain 3D organoid model. These studies helped to identify molecular mechanisms in the study of AD pathology and expanded research studies of the human brain which often could not be achieved through traditional animal models due to the inter-species differences that may exist. Most importantly, these organoid models offer potential for drug discovery and stem cell transplantation for the treatment of AD.

Although the use of stem cell therapy for the treatment of AD is still in the early stage of research, there have been some preliminary studies, including a phase I clinical trial by Korean scientists on nine patients with mild-to-moderate AD. In the trial, they injected different doses of human umbilical cord mesenchymal stem cells into two hippocampi and the right precuneus. Post-surgery wound pain, dizziness, delirium, and other obvious symptoms have nothing to do with the injection dose. All the symptoms

disappeared 1 week after the operation, and no other side effects occurred, such as cerebral hemorrhage[68]. In 2021, the research team injected different doses of human umbilical cord mesenchymal stem cells into AD patients' lateral ventricles. Symptoms, such as fever, headache, and nausea, occurred after surgery. Thirty-six hours later, the above-mentioned symptoms disappeared, and no other side effects occurred. They continued working on Phase II clinical trials for further in-depth research on stem cell therapy for AD[1].

Challenges are inevitable in the study of stem cell therapy for AD. For one thing, national policies exert a direct impact on the development of stem cell research in AD. However, different countries have varying policies on stem cell research based on factors, such as ethics, culture, religion, and public attitudes. For example, the Japanese government has a supportive stance toward stem cell research and has formulated a long-term plan to ensure adequate funding and legal oversight for the field[69]. The Chinese government also carried out policies in 2020 providing financial support to promote stem cell research and its transition into clinical practice[70]. However, the policies of the United States have been inconsistent in different periods. During the Bush period, the regulation of stem cell research was relatively strict, but during the presidency of Obama, the research in this field was relatively loose[71]. Changes in policy can have negative impacts on the stability and continuity of long-term research. For another, the specificity of stem cells themselves made the relevant research difficult. First, it would be hard to decide which type of stem cells to choose due to their various effects, how to improve the stem cell homing after transplantation, and how to control the differentiation *in vivo* after transplantation. Secondly, determining an appropriate dosage of stem cell transplantation is also a challenge. Although the Korean research team has concluded from their phase I and II clinical trials that the dosage of stem cells has nothing to do with adverse events, further clinical verification is needed. The identification of pathways to stem cell transplantation is challenging too. Intracranial transplantation of stem cells can bypass the blood-brain barrier and increase the density of stem cells in the brain, but it may bring trauma to the patients. Thus, superb transplantation techniques are necessary to complete such treatments. Vein grafting would be an ideal choice because such a method is simple, and its feasibility is high. However, as shown by animal models of AD, when being intravenously transplanted, stem cells enter the pulmonary circulation, where most of the stem cells are intercepted by pulmonary microvessels. This prevents the majority of the stem cells from reaching the brain lesion[72]. Finally, considering the individual differences of patients, the different stages of the disease, and the various pathological mechanisms, further verification is needed on whether transplantation would cause changes in the function of other cells, whether there would be immune rejection in allogeneic and/or in autologous transplantation, etc. to ensure the safety and effectiveness of stem cell therapy.

In conclusion, although stem cell therapy for AD currently faces several challenges, the progress in science, technology, and ongoing research suggests that it has the potential to become an effective treatment for AD. With further advancements, stem cell-based therapies and targeted drugs specifically designed for stem cell applications are expected to be realized soon, offering new hope for AD patients.

4.4. Strengths and limitations

This study offered valuable insights into the current research trends and hotspots concerning stem cells and AD. However, it is important to acknowledge

the limitations of this study. One limitation is the exclusion of articles published in languages other than English, which may have resulted in the omission of high-quality research. Additionally, the data were selected exclusively from the WoSCC database, thereby potentially excluding relevant studies indexed in other databases such as PubMed and Embase. Consequently, the findings may not fully represent the complete landscape of research in this field. Nonetheless, the WoSCC database is highly respected and widely used for bibliometric studies, providing reliable and influential data. Finally, it should be noted that the 2022 dataset was not included in this study as it is still being updated, which may have impacted the comprehensiveness of the findings.

5. Conclusion

Based on the analysis of the WoSCC database, the research on stem cells in AD reveals promising prospects and demonstrates an increasing trend over the years. Currently, the research on using stem cells for AD is primarily in the experimental stage, with only a few medical institutions conducting clinical studies on stem cell-based treatments for AD. However, the use of induced pluripotent stem cell models for studying AD is expected to be a major research direction in the future.

Acknowledgements

This research project was supported by the Guangxi University of Traditional Chinese Medicine Postgraduate Education Innovation Project (Grant No. YCBXJ2022009); Guilin Science and Technology Bureau (Grant No. 2020011208-5); National Natural Science Foundation of China (Grant No. 81973768).

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探索干细胞在阿尔茨海默病的研究前景: 2002–2021年文献计量分析

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摘要: 随着干细胞在阿尔茨海默病的研究越来越多, 这项研究已经成为该领域的研究热点。干细胞疗法是最具前景的一种治疗方法。本研究通过文献计量学可视化分析, 以探索干细胞在阿尔茨海默病的研究热点和趋势。构建干细胞对阿尔茨海默病研究的检索式, 数据来自Web of Science Core Collection database, 使用Cite Space和VOS viewer软件对2002至2021年的文献数据进行分析。干细胞对AD的研究涉及94个国家/地区, 共有3629个机构参与, 每年呈上升趋势, 其中美国和中国是主要的研究国家。Takahashi团队首次培养出诱导多能干细胞, 成为众多研究者理论的来源。University of California System是研究成果影响最大的机构, *Plos One*是最受欢迎的期刊, Maiese发现SIRT1是AD的治疗靶点, 并且他的研究成果最多。研究重点包括Brain, Dentate gyrus, Amyloid-beta, Oxidative stress, Neurodegeneration, Inflammation, Pluripotent stem cells, Neural stem cells, Microglia。我们的研究揭示了干细胞在AD中的全球研究趋势, 目前研究的热点是诱导多能干细胞模型在AD中的研究, 为该领域的研究工作者提高了重要的信息和参考。

关键词: 干细胞; 阿尔茨海默病; 文献计量学; 研究热点