

Bibliometric Analysis of Circular RNA Research on Stem Cells: A Swiftly Expanding and Shifting Focus

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Research

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Abstract

Background: The important roles of circular RNA in various aspects of the stem cell field have been gradually reported. This is the first time in recent decades that quantitative and qualitative evidence from bibliometrics has been used to conduct an in-depth analysis of circRNA in stem cell research to reveal relative research progress, trends and hotspots.

Methods: Publications from 1999 to August 7, 2021 were retrieved from the Web of Science Core Collection (WoSCC). All statistical analyses were performed using VOSviewer, CiteSpace and GraphPad Prism 7.

Results: The study shows that the number of papers on circRNA in stem cells has increased significantly since 2016. Among all types of papers, articles are the most published paper types, followed by reviews. Worldwide, published papers come mostly from China, followed by the USA, Germany, and Italy. However, Israel and Iran ranked first per million people and per trillion gross domestic product (GDP), respectively. The keyword analysis results were stratified into four clusters by VOSviewer software: Cluster 1, “cancer treatment”; Cluster 2, “function and effect”; Cluster 3, “characteristics” and Cluster 4, “osteogenic differentiation”.

Conclusions: Our results suggest that attention should be drawn to the latest hotspots, such as extracellular vesicles, ceRNAs and osteogenesis. In addition, suggestions on research directions and investment trends are provided to researchers and institutions.

Introduction

Circular RNAs (circRNAs) are a novel class of noncoding RNAs with a special covalent loop structure without a 5' cap and 3' tail^[1]. CircRNAs are widely present in various organisms, including the most recent common ancestors in fungi, plants, and eukaryotes^[2]. Generally, circRNAs are more stable than associated linear mRNAs in vivo. In some cases, the abundance of circular molecules exceeds more than ten times that of associated linear mRNAs^[3]. In 2013, Sebastian Memczak et al.^[4] detected thousands of well-expressed, stable circRNAs from human, mouse and nematode RNA. Sequence analysis indicated important biological regulatory functions for circRNAs. Since then, there has been an upsurge in studying the biological functions of circRNAs. In the same year, Thomas B Hansen et al.^[5] revealed the first circRNA with a specific biological function—ciRS7—which contains more than 70 selectively conserved miRNA target sites. Further studies have shown that circRNAs are involved in the occurrence and development of various diseases^[6–9] and play especially important roles in regulating tumor proliferation, migration, drug resistance and stemness^[10–13].

Stem cells are self-renewing cells that can differentiate into specialized cell types.^[14] There are three types of stem cells in the laboratory: embryonic stem cells, adult stem cells and induced pluripotent stem cells. Due to the particularity of their functions, stem cells have long been popular research objects in

regenerative medicine and clinical treatment of various diseases. Stemness refers to stem cell-like characteristics, the research related to which is mainly focused on cancer-related fields. For example, tumor stemness refers to cancer stem cells (CSCs) that have stem cell-like characteristics^[15]. Studies have demonstrated that tumor stemness does have a prominent effect on regulating tumor proliferation, metastasis and drug resistance^[16]. Furthermore, circRNA, as an important regulator of gene expression, has been proven to play an important regulatory role in many fields related to stemness^[17]. In terms of cancer, circRNAs can be specifically expressed in cancer tissues and regulate tumor stemness, proliferation, drug resistance and other characteristics. In terms of stem cell differentiation, Xiao Zheng et al.^[18] performed an in-depth review on the essential influence and internal mechanism of circRNAs involved in stem cell differentiation. In short, the analysis of stem cell growth and differentiation mechanisms and clinical treatment methods from the perspective of circRNA has become a new focus of research in recent years. However, due to the limitations of the search method, evaluation in the field from a holistic perspective has been difficult to achieve. Therefore, it is necessary to find a new method to learn more about the research status and hot trends of circRNAs in the field.

Bibliometrics is an interdisciplinary subject based on published literature and its references through mathematical and statistical methods for quantitative analysis^[19]. Research trends on specific subjects or academic impacts of publications can be assessed and predicted by bibliometric analysis. This article will use bibliometrics to explore the correlation between circRNAs and stem cells and summarize the types of papers and the distribution of authors, publishers and research hot spot trends. The main purpose of this article is to provide suggestions on scientific research topics, cooperative institutions or submitted journals for related researchers and institutions.

Materials And Methods

Data source and search criteria

A comprehensive bibliographic retrieval was accomplished online through the Web of Science Core Collection (WoSCC) on 3 August 2021, which was performed on a single day to avoid daily updating bias since the database was still open.

All the search keywords referred to MeSH terms from PubMed except “stemness”, which was irreplaceable but could not be obtained in the MeSH terms. The search terms were as follows: (((circRNA OR circRNAs) OR closed circular RNA) OR circular RNA) OR ciRNA) AND (((stemness OR stem cell) OR stem cells) OR progenitor cell). The time period of article publication was from 1 January 1999 to 3 August 2021. The export record contents were Full Record and Cited References, and the file format was Tab-delimited (Win, UTF-8).

Analysis method

VOSviewer (version 1.6.16.0) and CiteSpace (5.7. R5) were used to analyze the document types, publication years, authors, cocited authors, journal source titles, countries, keywords and research areas to form network maps^[20]. The original data extracted from WoSCC were imported into Microsoft Excel 2010 to conduct data aggregation and preliminary analyses. The time trend of the number of publications was graphed with GraphPad Prism 7 software. Considering the differences in aggregate economic volume and population among countries, the latest information on population and gross domestic product (GDP) was obtained from the World Bank website [<https://data.worldbank.org>].

Results

Paper type and quantity

The research flow chart of our study is shown in Figure 1. A total of 504 records that met our inclusion criteria were identified in this study. The records were classified as 9 types (Fig. 2A). Articles (64.22%) accounted for the largest proportion of all records, followed by review articles (32.41%). Therefore, we will focus on these two types of papers in the following analysis.

Fig. 2B displays the number of papers and the exponential trend line over time, which can reflect the relationship between the publication year and the number of publication records to a certain extent. The data show that the first paper among all selected papers was published in 1999, and the number of papers in related fields was relatively low (no more than 10) until 2015. Since 2016, however, the number of published papers has just risen rapidly. A total of 274 papers were published in the past two years, accounting for 73.27% of all the selected papers.

Moreover, we also determined the first five research fields with the most published papers in Table 1. Among them, the first area was the field of cell biology (27.63%), followed by biochemical molecular biology (20.48%), research experimental medicine (18.49%), oncology (18.29%), and genetics heredity (9.74%). The quantity of papers in other related fields, such as Biotechnology Applied Microbiology and Pharmacology Pharmacy, is also continuing to increase.

Author, organization, country and funding agency

A total of 3027 authors were included in this study. Table 2 shows the top ten and cocited authors according to the numbers of papers and citations. China was the main distribution with the most researchers in the related field, followed by the USA, Germany, and Italy. Among authors in China, and were the main contributors.

In terms of organizations, a total of 637 research institutions were included in this study. The top 3 organizations with the most contributions are displayed in Fig. 2C, which are all from China. The top one is Nanjing Medical University, with 22 related papers, followed by Shanghai Jiao Tong University (21 papers) and Sun Yat-sen University (20 papers). Furthermore, close collaborative connections between

various institutions were also identified. The Chinese Academy of Science is ranked first, having 16 links with other institutions, followed by Shanghai Jiao Tong University (12 links) and Sun Yat-sen University (11 links). The data also showed that the collaborations among Chinese universities were very close. Frequent exchanges occurred between Peking University, Tongji University, Central South University and China Medical University. These bibliometric network maps can provide reliable information about influential institutions, which can help researchers or students be more convinced when making a related decision.

All the papers were from 40 countries. Regarding the research strength of the countries, China (332 papers) was the most productive country, accounting for 63.85%, followed by the USA (86 papers, 16.54%), Germany (24 papers, 4.62%) and Italy (20 papers, 3.85%). Table 3 shows that after adjustment by population, Israel was first with 0.86 papers per million people. After adjustment by GDP, Iran ranked first, with 41.76 papers per trillion GDP, followed by China, with 22.55 papers per trillion GDP. Fig. 2D shows the 22 most productive countries in terms of the quantity of papers and the collaboration situation. The color of the node represents a different cluster, and the size of the node represents a different number of papers, with larger nodes meaning more papers. The collaborations among various countries were very close. The connections between Western European countries and the relationship between China and other countries were relatively obvious.

The top 10 funding agencies are shown in Table 4, which are ranked by the number of papers. Half of the top 10 funding agencies are based on China. The National Natural Science Foundation of China endorsed 206 papers in this field (ranked first, 40.95%), followed by the National Institutes of Health (45 papers, 8.95%) and the United States Department Of Health and Human Services (45 papers, 8.95%).

Publication distribution of journals and cocited journals

Currently, research on the stemness of circRNAs has been published in 269 journals, and the top 10 journals were selected according to the number of published papers. The publishing countries, the number of citations and the impact factor (IF) in 2020 are listed in Table 5. The journal with the most published papers was *Molecular Cancer*, which published 11 related papers, with 504 citations. Four of the top 10 journals are British journals, ranked 1 and 2. The United States had three journals, followed by Switzerland (2 journals) and Greece (1 journal). The table also shows that the ranking of the number of papers has some disagreement with the ranking of the number of citations. Based on the number of citations and the IF, the authority of the journals *Journal of Experimental Clinical Cancer Research* and *Molecular Therapy Nucleic Acids* is relatively high, although they were not ranked in the top three. Furthermore, "citation/N" represents the average citations per paper. *Molecular Cancer* ranked first, with 11 papers and 504 citations, meaning that each paper was cited an average of 48.51 times.

Table 5 also shows the names, total citations, publishing countries, and IF of the top 10 cocited journals. *Nature* from the UK ranked number one with 1476 citations and an impact factor of 49.962,

followed by *Cell* from the USA (1330 citations, 41.58 IF). Among these ten journals, 6 were based in the US, and 4 were based in the UK.

Co-occurrence keywords and burst keyword analysis

All the keywords extracted from 505 papers were identified and analyzed. Fig. 3A shows the density visualization based on the keywords. The color of each point in a map depends on the density of items at that point. The warm red color represents hot and important areas, and the cool blue color represents cool areas. According to the order of occurrence of the keywords, the main hot keywords are circular RNA, expression, stem cells, proliferation, identification, cancer, differentiation, microRNA, etc. (similar keywords removed).

Fig. 3B shows the overlay visualization result, with keywords from inception (1999) to 2020. According to the legend in the lower right corner, the yellow node indicates the new and emerging point, while the purple node indicates the old point before 2015. It is obvious that the majority of the keywords have emerged in the last 3 years, which reflects that the stemness of circRNA is an emerging field. Furthermore, Fig. 3C shows the network visualization with 4 clusters, which were classified by different node and wire colors. The size of the nodes in the figure represents the importance of the keywords.

Cluster 1 focuses on the autophagy, chemoresistance and ceRNA network of circular RNA. Part of this cluster also involves the relationship between stem cells and circRNAs and their role as tumor suppressors for certain cancers. From Fig. 5a, Cluster 1 is a mainly emerging research field. Cluster 2 was also new in time, and the keywords with the highest frequency were expression, cancer, proliferation, metastasis and biomarkers. Clusters 1 and 2 both reveal the importance of circRNAs in cancer, which is currently the hottest field. In contrast, Cluster 3 is a relatively early and mature research field that focuses on the identification, transcription and biogenesis of circular RNAs and embryonic stem cells. Cluster 4 revolves around mesenchymal stem cells, osteogenic differentiation and exosomes, which is also a new direction in research.

Fig. 3D can be used to identify the hot topics. The red line in the figure represents the time period with the strongest citation bursts. The first keyword is embryonic stem cells, which appeared in 2016. Later, translation, expression, differentiation and migration became hot keywords. All the top keywords had the strongest citation after 2016, demonstrating that this is an emerging field.

To make the result more convincing, the analysis of keyword co-occurrence in CiteSpace was also conducted. The visualization result is shown in Fig. 4A. Each node in the figure represents one keyword, and the node size indicates the frequency of the keywords; the larger the circle is, the higher the frequency. Careful comparison shows that the result is highly similar to the one we obtained in VOSviewer. Fig. 4B clearly shows the top 8 clusters from all the keywords: circular RNA, neural stem cell,

miRNAs, lncRNAs, etc. Furthermore, Fig. 4C and Fig. 4D can make it more intuitive to see the research status of each cluster at different time nodes.

Discussion

This article conducts a preliminary analysis of keywords in the selected literature at the intersection of circRNAs and stem cells. Eighty keywords were divided into 4 clusters by the network visualization of VOSviewer. Cluster 1 had a close relationship with Cluster 2, mainly keywords related to “tumor” and “treatment” (including specific tumor name), such as tumor suppressors and biomarkers. Cluster 3 is mainly related to the “characteristics” of circRNA and stem cells themselves, such as biogenesis, transcripts, and noncoding RNA. Cluster 4 mainly contains keywords related to the direction of “osteogenesis differentiation”.

In recent years, research hot spots at the intersection of circRNAs and stem cells have generally shifted from Cluster 3 to Clusters 1 and 2. From the result of our overlay visualization, researchers focused on the source, composition, classification in vivo and differentiation and expression of embryonic stem cells. However, in the past two years, the main research focus has shifted to the fields of tumorigenesis, development and clinical treatment. According to our keyword co-occurrence analysis, both circRNAs and stem cells are closely related to the proliferation, metastasis and drug resistance of tumors. Among the keywords, “circRNA” and “biomarkers” have a link strength of 15, which indicates that circRNA has a promising future in the direction of emerging biological targeting drugs. Furthermore, the connection between circRNA and stem cells is very close (link strength: 40). In addition, the study of circRNA involvement in stem cell differentiation and expression is also a new hot spot.

Cancer (here generally referring to all malignant tumors) is the main cause of death in all countries around the world, and it is also one of the high-frequency keywords screened in this study. Among all types of cancers, cancers of the female breast, lung, colorectum, and prostate comprised 62% of the total cancer burden in medium to very high HDI (Human Development Index) areas^[21]. The numbers of cancer cases and deaths are expected to increase rapidly as populations grow, age, and adopt lifestyle behaviors that increase cancer risk^[22]. Therefore, it is particularly important to find new methods for the prevention, early detection, and effective treatment of the abovementioned high-risk cancers. CircRNAs have shown great potential in the treatment and prognosis of cancer because they are widely expressed in eukaryotes and highly stable^[22]. On the one hand, circRNAs can be used as a new type of biomarker to monitor the progress of specific cancers; on the other hand, they can also regulate cancer proliferation, metastasis or drug resistance through ceRNA network mechanisms. Similarly, the heterogeneity and plasticity of stem cells also make them play an important role in tumor development. They can produce organoid structures to mimic human disease models^[23]. In addition, transgenic stem cell transplantation is also a potential cancer treatment^[24]. From our research, it is intuitive that the keyword “cancer” has a frequency of 57 and a total connection strength of 289. It is closely related to both circular RNA and stem cells, which is more

in line with the current research status. This also shows that circRNAs and stem cells have good research prospects in cancer-related fields, which are worthy of further research and exploration.

In addition to analyzing keywords, we also conducted a further analysis of article types, research institutions, published journals, and the distribution of countries where articles were published. According to the results, the proportion of reviews is relatively high (32.41%), which reflects that researchers may have made many sorts and summaries on the basis of existing research to assist further studies. This proves the necessity of bibliometric analysis because great importance is attached to the summary of this field. The high number of reviews is a major advantage for new researchers, as they can gain a more comprehensive understanding of the directions of research. However, it also means new research is scarce, and we need to bring in talent for further and in-depth research.

Currently, the most influential institutions in related fields in China are Nanjing Medical University, Shanghai Jiao Tong University, and Sun Yat-sen University, which are mainly concentrated in southeastern China. The information is very useful for students and scholars interested in this field so that they can choose where to study or become employed at home and abroad.

For the published sources, *Molecular Cancer* from the UK had published the most papers (11 papers), with the highest number of citations (504) and highest impact factor (27.401). These results indicate that researchers must have a good judgment of the journals' preferences when submitting related articles. Further studies can be guided for submission to these journals.

In regard to analysis by country, China and the USA were the most productive countries, and the H-index and total citations of China were both ranked first. However, when considering GDP, Israel and Iran's research strengths were relatively high. This indicates that developing countries still have a certain influence in the international arena. Developing countries should take into account the development of economic and scientific research capabilities.

Conclusion

The number of publications regarding circRNA in stem cell research has been constantly growing since 2016, and we predict that it will continue to rise. Mainland China and the USA were found to be the most productive regions. The most popular keywords at this stage mainly focus on tumorigenesis and clinical treatment, meaning that funding agencies could increase investments in exploring the clinical diagnosis and treatment potential of circRNAs in stem cell research. It is also recommended that more attention be paid to the latest promising hotspots, such as "expression", "proliferation", "identification", "cancer", "differentiation", and "microRNA".

Declarations

•Ethics approval and consent to participate

Not applicable

•Consent for publication

Not applicable

•Availability of data and materials

The datasets supporting the conclusions of this article are available in the WOSCC repository, [unique persistent identifier and hyperlink to dataset(s) in <http://apps.webofknowledge.com>]

•Competing interests

The authors declare that they have no competing interests.

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•Authors' contributions

S.Y.L: collected, analyzed the data and wrote the manuscript, contributed to the revision of the manuscript. C.W.L: conceived the researching theme, edited and approved the reversion of this paper for submission and participated in the finalization of the manuscript. F.L, L.Y.W, X.H.Z: contributed to the revision of the manuscript. All authors read and approved the final manuscript.

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Not applicable

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Tables

Table 1

The top 10 research area for circRNA in stem cell (n%).

Research areas	N	%
Cell Biology	139	27.63%
Biochemistry Molecular Biology	103	20.48%
Research Experimental Medicine	93	18.49%
Oncology	92	18.29%
Genetics Heredity	49	9.74%
Biotechnology Applied Microbiology	36	7.16%
Pharmacology Pharmacy	26	5.17%
Science Technology Other Topics	25	4.97%
Developmental Biology	21	4.18%
Hematology	20	3.98%

Table 2

The top 10 authors and co-cited authors for circRNA in stem cell research.

Rank	Author	Country	Document	Co-cited author	Country	Citation
1	Kjems, jorgen	Denmark	4	Hansen,tb	Denmark	302
2	Liu, jinbo	China	4	Memczak,s	Germany	224
3	Sun, zhenqiang	China	4	Jeck,wr	USA	189
4	Yuan, weitang	China	4	Salzman,j	USA	170
5	Zhou, quanbo	China	4	Zhang,y	China	160
6	Hansen, thomas b.	Denmark	3	Du,ww	Italy	122
7	Abdelmohsen, kotb	USA	3	Chen,ll	China	110
8	Gorospe, myriam	USA	3	Wang,y	China	101
9	Wang, guixian	China	3	Ashwal-fluss,r	Israel	100
10	Wang, weiwei	China	3	Zhang,xo	China	93

Table 3

The top 10 countries for circRNA in stem cell research (n%).

Country	N	%	N per million people	N per trillion GDP	H-index	Total citations
China	332	63.85	0.24	22.55	38	5354
America	86	16.54	0.26	4.11	30	4106
Germany	24	4.62	0.29	6.31	11	1319
Italy	20	3.85	0.34	10.60	10	1339
England	15	2.88	0.22	5.54	8	389
Japan	12	2.31	0.10	2.37	7	646
Iran	8	1.54	0.09	41.67	4	96
France	8	1.54	0.12	3.07	5	89
Israel	8	1.54	0.86	19.90	5	198
Australia	7	1.35	0.27	5.26	4	128

Table 4

The top 10 funding agencies for circRNA in stem cell research (n%).

Rank	Funding agency	N	%
1	National Natural Science Foundation Of China	206	40.95%
2	National Institutes Of Health	45	8.95%
3	United States Department Of Health Human Services	45	8.95%
4	China Postdoctoral Science Foundation	22	4.37%
5	National Key Research And Development Program Of China	19	3.78%
6	European Commission	16	3.18%
7	Nih National Cancer Institute	15	2.98%
8	German Research Foundation	14	2.78%
9	Fundamental Research Funds For The Central Universities	13	2.58%
10	National Natural Science Foundation Of Guangdong Province	13	2.58%

Table 5

The top 10 journals and co-cited journals for circRNA in stem cell research.

Rank	Journals	Country	N	IF (2020)	Citations	Citation/N (average citation)	Co-cited journal	Co-citations	Country	IF (2020)
1	Molecular Cancer	UK	11	27.401	504	45.81	Nature	1476	UK	49.962
2	Stem Cell Research & Therapy	UK	11	6.832	136	12.36	Cell	1330	USA	41.582
3	International Journal of Molecular Sciences	Switzerland	10	5.923	49	4.90	Nucleic Acids Research	823	UK	16.971
4	Frontiers in Cell and Developmental Biology	Switzerland	10	6.684	36	3.60	Proceedings of the National Academy of Sciences of the United States of America	796	USA	11.205
5	Cell Death & Disease	UK	9	8.469	171	19.00	Molecular Cell	791	USA	17.970
6	Journal Of Experimental Clinical Cancer Research	UK	9	11.161	310	34.44	PLoS One	749	USA	3.240
7	Biomed Research International	USA	8	3.411	55	6.88	Science	631	USA	47.728
8	Molecular Medicine Reports	Greece	7	2.952	37	5.29	Oncotarget	562	USA	5.168
9	Molecular Therapy Nucleic Acids	USA	7	8.886	126	18.00	Nature Communications	559	UK	14.919
10	Aging Us	USA	6	5.682	21	3.50	Scientific Reports	548	UK	4.379

Figures

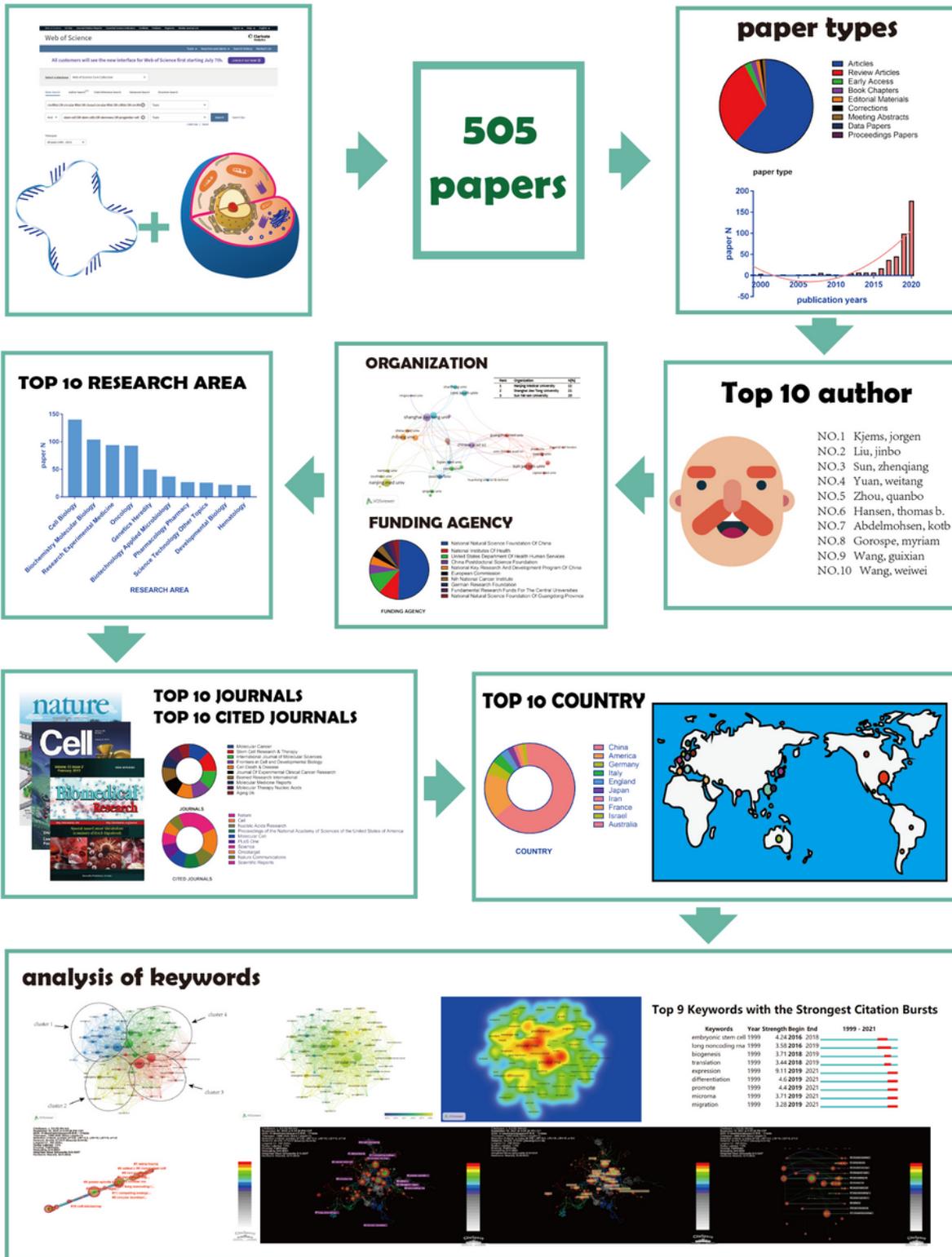


Figure 1

Flow chart of the research design and the main results.

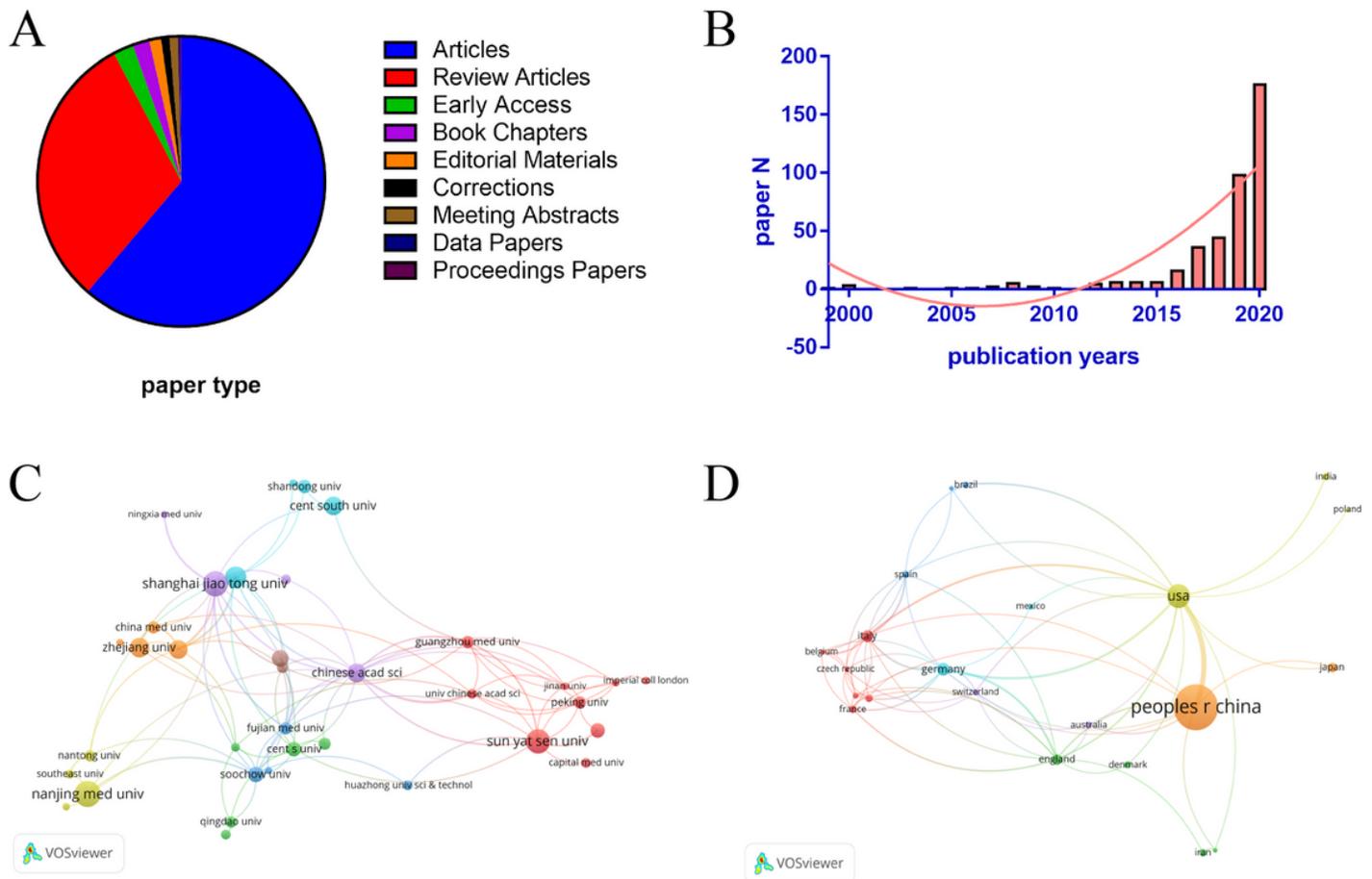


Figure 2

The contributive characteristics and mapping of organizations and countries involved in circRNA-related stem cell research. (A) The document type percentage of reports for circRNA in stem cell research. (B) Model fitting curves of growth trends of the accumulated number of publications for circRNA in stem cell research. (C) Network visualization map of the top 36 institutions. (D) Network visualization map of the most productive countries for circRNA in stem cell research.

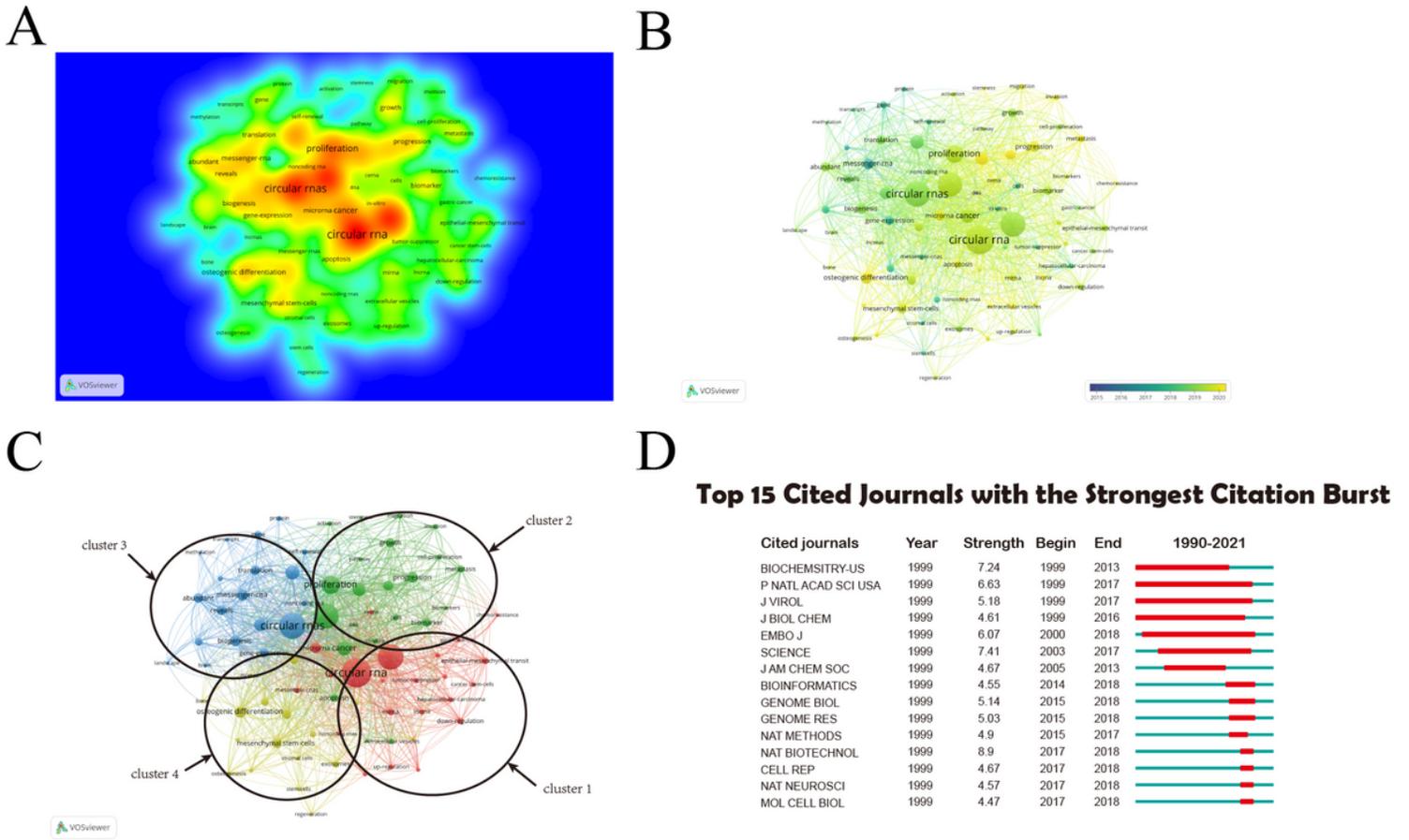


Figure 3

Bibliometric analysis of circRNA keywords in stem cell research. Density visualization (A), overlay visualization (B), network visualization (C) and the top 9 keywords with the strongest citation burst (D) are shown. The color in (A) represents the density of keywords, warm red color indicates hot and important areas, and keywords with close distances are more related to each other. The node size in (B, C) is based on the occurrence frequency of the corresponding keywords, and the node color in (B) represents the average publication year. Keywords in blue are presented earlier than those in yellow. In (D), the red line in the figure represents the time period with the strongest citation bursts.

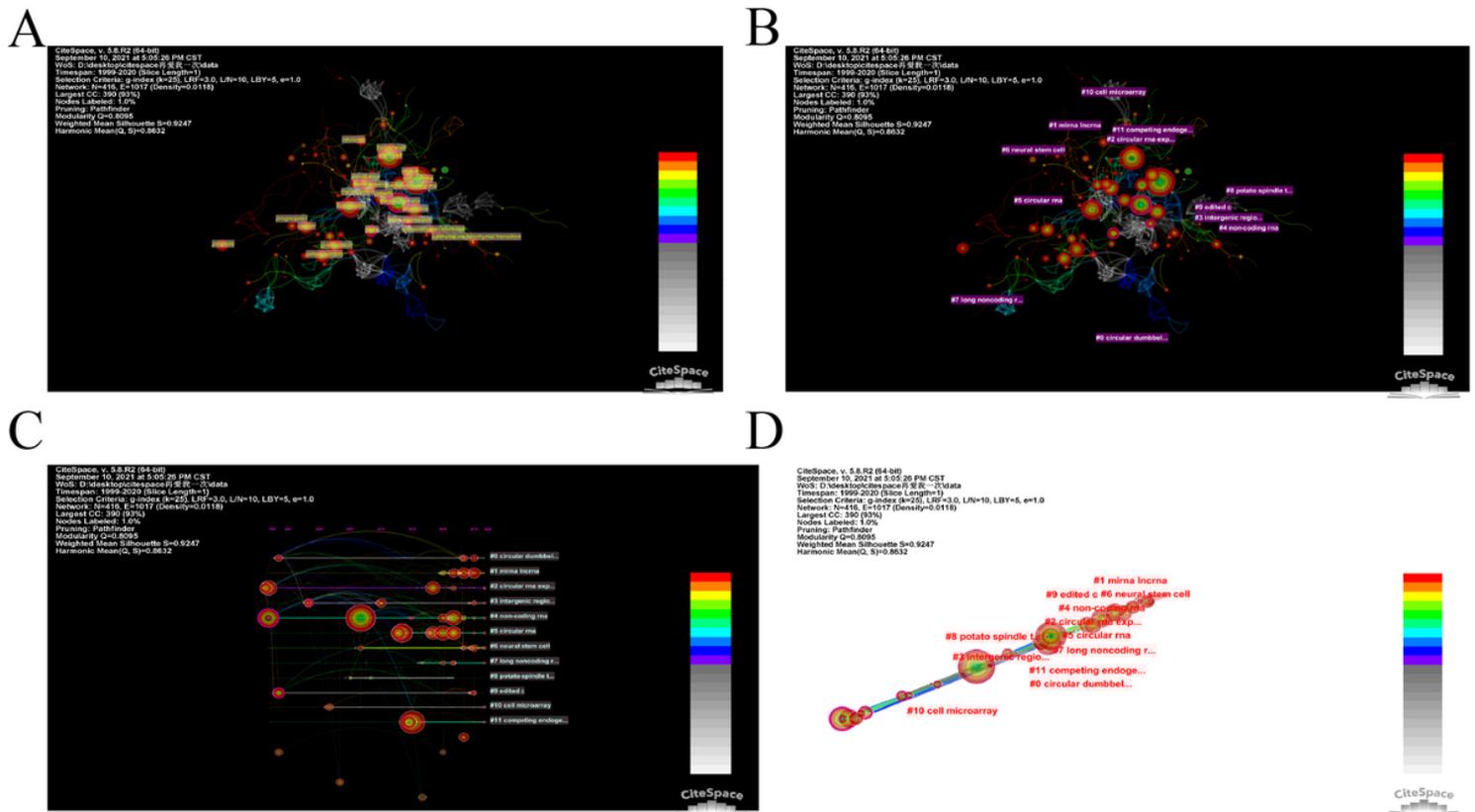


Figure 4

Mapping of CiteSpace analysis of keywords of circRNA in stem cell research. Network map (A), cluster view (B), timeline view (C) and timezone view (D) of co-occurring keywords for circRNA in stem cell research.