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REVIEW

Mapping the Knowledge Landscape of and Emerging Future Trends in Stem Cell Therapy for Osteoarthritis: A Bibliometric Analysis of the Literature From 1998 to 2024

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Video Abstract

Point your SmartPhone at the code above. If you have a QR code reader the video abstract will appear. Or use: https://youtu.be/KqcQxa6qQCA

Objective: The purpose of this study was to conduct a bibliometric analysis of the literature on stem cell therapy for osteoarthritis (OA) to visualize recent developments, identify hot spots, and determine trends in the field.

Background: OA is a chronic disease that affects the joints and their surrounding tissues, leading to progressive damage to the articular cartilage and ultimately to the subchondral bone and the surrounding synovial structures. OA is a disabling disease with an increasing incidence and prevalence in the general population. Modulation of immunity and inflammation and improvement of cell survival and differentiation through multidirectional differentiation of stem cells is a potential strategy for the treatment of OA.

Methods: We searched for publications on "stem cell therapy for osteoarthritis" in the Web of Science (WOS) core collection database from 1998–2024 and summarized the results, including year of publication, country, institution, author, and collaborative network generated using VOSviewer and Citespace. In addition, research trends were identified. Finally, we summarized the hot topics and identified future research trends.

Results: This study ultimately included 2341 valid papers, with a trend toward a gradual increase in the number of publications over time. The country, institution, author, and journal with the highest number of publications and citations were China, the University of California system, Sekiya I, and Osteoarthritis and Cartilage, respectively. High-frequency keyword clusters included cell therapy, stem cells, tissue engineering, and extracellular vesicles.

Conclusion: Through visualization and analysis, we elucidated the trends and research hotspots in the field over the past five years. The analysis revealed that stem cell transplantation and exosome therapy for OA may be the focus of future research. This study lays the foundation for future research and clinical work on stem cell therapy in this field.

Keywords: osteoarthritis, stem cell, tissue engineering, exosome, extracellular vesicles, bibliometric analysis, VOSviewer, citespace

Introduction

Osteoarthritis (OA) is a chronic disease that affects the joints and their surrounding tissues and is a leading cause of joint pain, loss of physical function and disability.[1] It is estimated that 10% of men older than 60 years and 18% of women older than 60 years will develop OA.[2] As one of the most common orthopedic diseases, OA not only imposes a heavy health and financial burden on patients but also impacts the healthcare system. As a result of intensive research, OA is no longer considered to involve simple cartilage degeneration; it also involves destruction of the subchondral bone, formation of excess bone, synovial inflammation and peripheral ligamentous and muscular changes.[3] Although some advances in the surgical and pharmacologic treatment of OA have been reported, effective repair of cartilage degradation

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remains a challenge in clinical management of patients with this disease. Stem cells reach specific regions of the body via vascular endothelial migration or mesenchymal migration and may participate in the repair of damaged cartilage.[4] Stem cells have self-replication, self-division, self-renewal and multidirectional differentiation ability, allowing them to repair tissues and maintain homeostasis in vivo.[5] They also exert immunomodulatory effects and paracrine effects via the synthesis and release of cytokines that stimulate the proliferation of progenitor cells, inhibit apoptosis and promote tissue repair. Stem cells exert paracrine anti-inflammatory and immunomodulatory effects via secretion.[6]

Bibliometric analysis has been widely used to analyze large amounts of scientific research data and identify trends. Importantly, it can be used to summarize the evolution of publications, predict research hotspots, and further assess the frontiers of a particular field through citation networks.[7] CiteSpace is a software tool that visualizes information to present and identify emerging trends. The software can present the structural relationships and evolutionary patterns of a research field in different dimensions and at different levels for beginners in the form of a knowledge graph. Moreover, the software is easy to access, easy to manipulate and readable.[8] VOSviewer takes a holistic view of all research objects and explores research themes across the field by selecting different viewpoints. In a previous study, bibliometric methods were used to determine the current status of stem cell research and its impact on OA treatment from 2001 to 2021, as well as future trends in OA treatment.[9] By including research on stem cells for the treatment of OA from database inception in 1998 to the present day, this study is more comprehensive in terms of the amount of literature and research findings. In addition, the types of stem cells used to treat OA are continually being expanded and now include neural stem cells, Schwann cells, olfactory ensheathing cells, bone marrow mesenchymal stem cells, and induced pluripotent stem cells. Therefore, an up-to-date bibliometric analysis of the literature is necessary and important.

The available research on stem cells in the field of orthopedic diseases focuses on clinical observations and mechanistic studies but lacks a clear compendium in terms of popular trends and intuitive structural displays. This study aims to analyze the application of stem cell therapy for OA through bibliometrics. Elements such as countries, authors, organizations, and keywords are presented in the form of a knowledge map to provide a comprehensive understanding of the research background of stem cell therapy for OA, to predict future research trends and hotspots, and to provide references for related research.

Materials and Methods

A search for publications related to stem cell therapy for OA was conducted in the WoS Core Collection (SCI-EXPANDED and SSCI) on July 1, 2024. The search formula was as follows: [TS= (osteoarthritis of the knee or osteoarthritis of the knee or koa or osteoarthritis of the knee or osteoarthritis of the knee)] AND [TS= (“stem cells“ or “stem cells“)]. The search period ended on June 30, 2024. The study types were limited to ”article” and ”review”.

First, a literature review was conducted using WoS to identify the annual outputs; countries; authors; journals; institutions and territories; and languages of the included studies. CiteSpace software (version 6.3. R1) and VOSviewer were used to identify the top authors, institutions, countries and collaborative networks. The CiteSpace parameters were set as follows: time slicing, 1998–2024; years per slice, 1; term source, all selections; node type, choose one at a time; selection criteria, top 50 objects; and pruning, pathfinder, pruning sliced networks.

Bibliometric network construction and visualization were performed using VOSviewer and CiteSpace. Comprehensive information about keyword cooccurrences, country/institutional collaborations, authors, etc., was captured in CiteSpace charts. For each node type, this information included node size (ie, frequency of occurrence or citation), internode centrality (labeled as an orange ring if ≥ 0.1, indicating a key node in the collaborative or cocitation network), outbreaks (purple rings), and clustering of important nodes. A connecting line between two nodes indicates the presence of collaboration (between countries/regions, authors, or institutions).[10]

Results

Bibliometric Analysis of Publications

Changes in the growth trend of publications indicate the developmental trajectory of a research field, and the number of publications is an important indicator for hot spot assessment. In this study, we retrieved 2341 publications on stem cell

therapy for OA from WOS; these studies were limited to the"Article" and "Review"categories (Figure 1). If a paper was coauthored by researchers from more than one country/region or institution, it was equally distributed to all participants. Figure 2 shows the annual research output between 1998 and 2024, when the initial research on stem cell therapy for OA was published. In some consecutive years, particularly after 2017, the growth rate rose rapidly. According to the WOS database, 82 countries or territories contributed to research publications on stem cell therapy for OA. A geo-visualization map was generated visualize the relationships among all the countries in the field. The size of the circles indicates the number of papers, and the line segments between the different circles indicate collaborations between countries; the thicker the line segments are, the greater the degree of collaboration (Figure 3). The top 10 funding sources are listed in

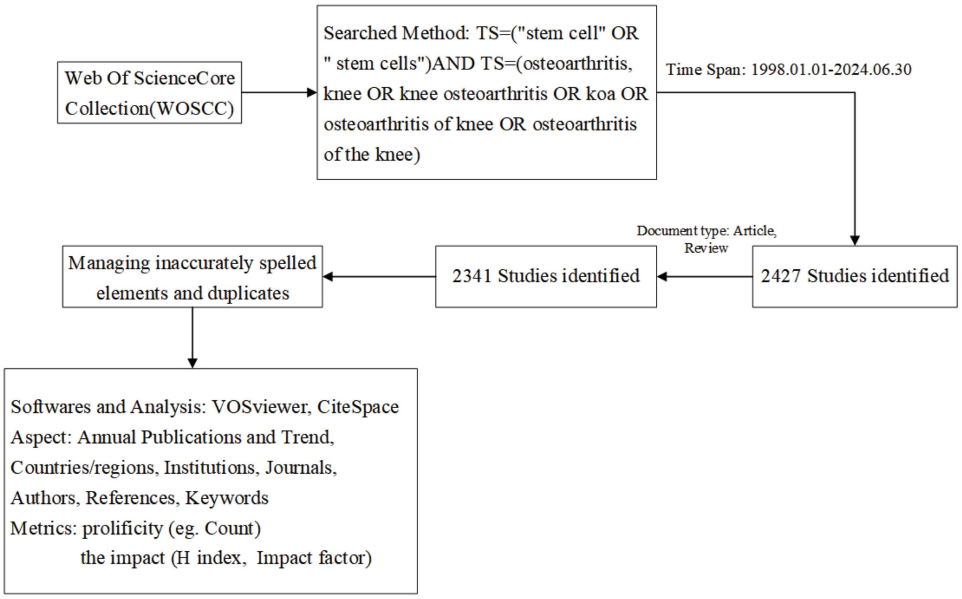

Figure 1 Flowchart of the process used to screen articles and systematic reviews for bibliometric analysis.

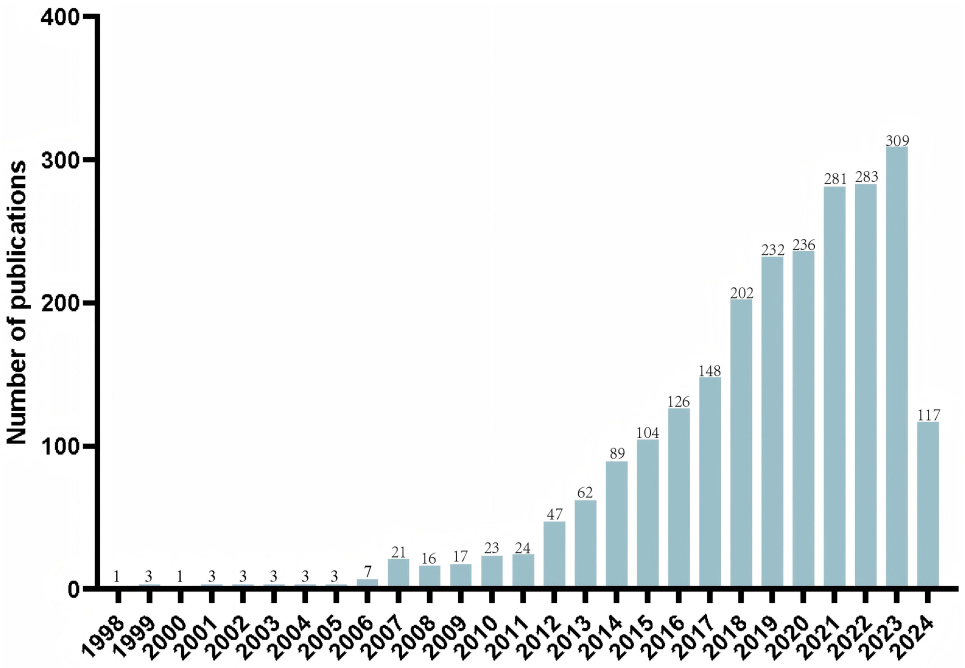

Figure 2 Distribution of literature on stem cell therapy for osteoarthritis from 1998 to 2024.

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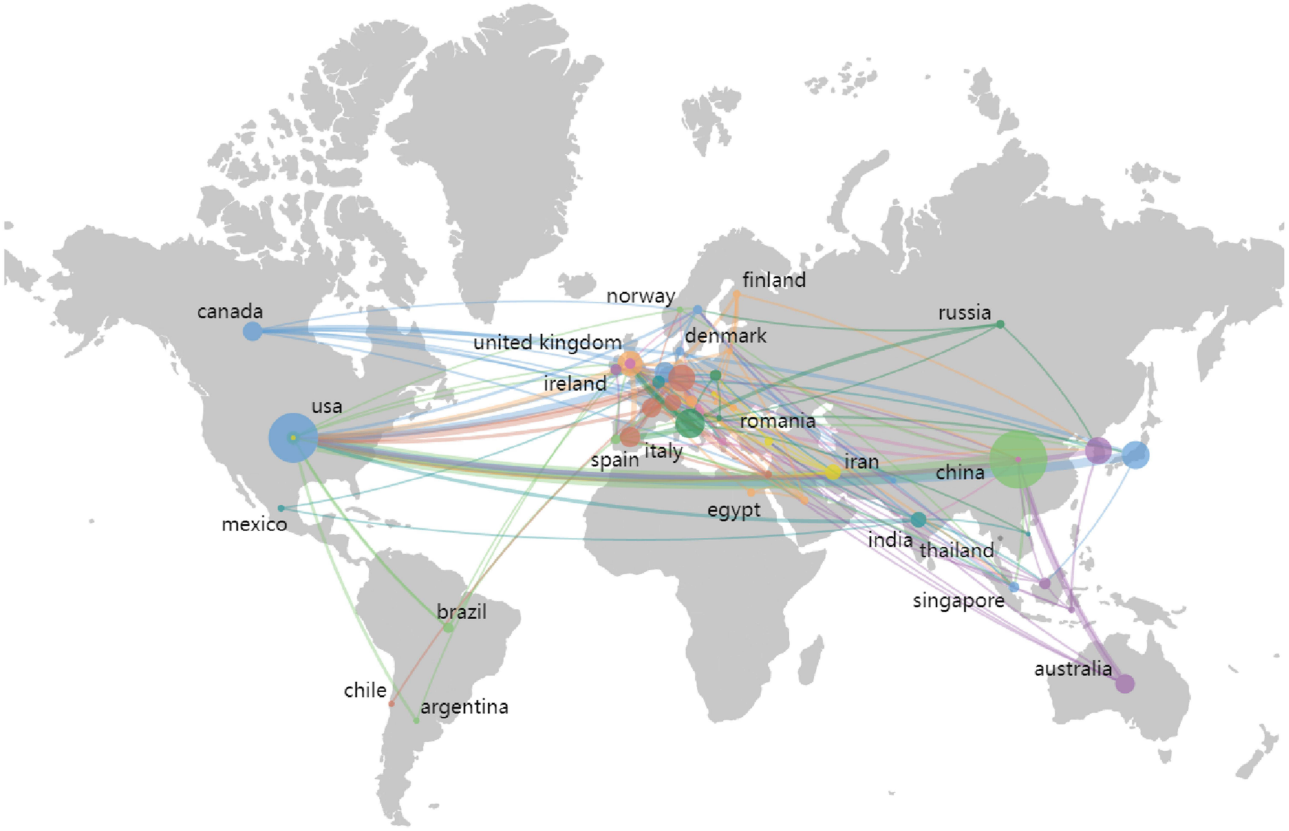

Figure 3 Distribution and collaborations of high-yield countries/regions. The line segments between different countries represent the intensity of collaboration, and the thicker the line segments are, the greater the intensity of collaboration.

Table 1, and the National Natural Science Foundation of China (NSFC), the United States National Institutes of Health (NIH) and the United States Department of Health and Human Services were the top 3 funding sources.

Journal Analysis

From 1998, when research on stem cell therapy for OA first started, to 2024, a total of 513 journals published literature on the subject, and Table 2 lists the top 10 journals with the greatest number of published papers. These 10 journals published 23.025% of the total studies. Osteoarthritis and Cartilage is the most active journal in this field, followed by the International Journal of Molecular Sciences. Among the journals with impact factors greater than 4.00, Osteoarthritis and Cartilage is the journal with the largest impact factor (IF =7.2). Articles published in a number of active professional

Table 1 Top 10 Funding Sources for Publications on Stem Cells for Osteoarthritis

Ranking	Found Source	Frequency	Ranking	Found Source	Frequency
1	National Natural Science Foundation Of China Nsfc	329	6	Grants In Aid For Scientific Research Kakenhi	67
2	National Institutes Of Health Nih USA	184	7	European Union EU	57
3	United States Department Of Health Human Services	184	8	UK Research Innovation Ukri	48
4	Ministry Of Education Culture Sports Science And Technology Japan Mext	77	9	Nih National Institute Of Arthritis Musculoskeletal Skin Diseases NIAMS	46
5	Japan Society For The Promotion Of Science	73	10	National Research Foundation Of Korea	33

Table 2 Top 10 Productive Journals That Contributed Publications on Stem Cells for Osteoarthritis

Ranking	Journal	Publications	Times Cited (Total)	Times Cited (per Article)	Time Cited (Average per Itm)
1	Osteoarthritis And Cartilage	90	7351	7302	81.68
2	International Journal Of Molecular Sciences	84	2242	2208	26.69
3	American JournaL Of Sports Medicine	70	3072	2984	43.89
4	Cartilage	54	924	922	17.17
5	Stem Cell Research Therapy	48	2324	2292	48.42
6	Journal Of Orthopaedic Research	43	1260	1255	29.3
7	Stem Cells International	41	1042	1027	25.41
8	Scientific Reports	40	1466	1463	36.65
9	Knee Surgery Sports Traumatology Arthroscopy	36	1577	1535	45.06
10	Arthroscopy The Journal Of Arthroscopic And Related Surgery	33	1899	1869	57.55

journals, such as Osteoarthritis and Cartilage, Stem Cell Research Therapy, Knee Surgery Sports Traumatology Arthroscopy, and Arthroscopy The Journal of Arthroscopic and Related Surgery, had an average of over 45 citations.

Contributing of Authors

There are approximately 10,480 authors who indexed 2341 articles related to stem cell therapy for OA. Table 3 lists the top 10 authors and their institutions, all of whom are experts in this field. Sekiya Ichiro from Tokyo Medical and Dental University has published 40 articles and is the most cited author (cited 1844 times); the second is Koga, Hideyuki, from Tokyo Medical and Dental University (32 articles, cited 1409 times); followed by Filardo, Giuseppe from Tokyo Medical and Dental University (28 articles, cited 1179 times). The author co-occurrence map was generated using CiteSpace. The h-index is a bibliometric parameter that measures both the quantity (number of articles) and quality (number of citations) of published papers and their growth over time.[11] Betweenness centrality measures the probability that a node is on the shortest path between two other points. The greater the internode centrality is, the more important the node. The centrality of different authors was 0, indicating that research in this field has not yet formed a widely connected core author network.[12] Figure 4A shows the largest coauthor subnetwork. The top three authors by co-occurrence are Sekiya, Ichiro; Koga, Hideyuki; and Filardo, Giuseppe, with H-indexes of 21, 18, and 18, respectively. Ranked by centrality, the top three authors are Sekiya, Ichiro; Koga, Hideyuki; and Filardo, Giuseppe (Figure 4B). Figure 4C shows the authors with the strongest explosive power in publishing papers in this field, whose number of published papers has increased rapidly over time; the top three authors are Filardo, Giuseppe; De Girolamo, Laura, and Muneta, Takeshi. The authors

Table 3 The Top 10 Active Authors With Most Publications From 1998 to 2024

Rank	Author	Publications	Institution	Time Cited	Time Cited (per Article)	H-Index
1	Sekiya I	40	Tokyo Medical and Dental University	1844	1692	21
2	Koga H	32	Tokyo Medical and Dental University (TMDU)	1409	1303	18
3	Filardo G	28	IRCCS Ist Ortoped Rizzoli	1179	1106	18
4	Muneta T	25	Tokyo Medical and Dental University	1677	1589	20
5	Tsuji K	24	Tokyo Medical and Dental University	1036	979	16
6	Kon E	23	Humanitas University	1138	1102	17
7	Li J	22	Guangzhou University of Chinese Medicine	351	348	12
8	De Girolamo L	20	Galeazzi Orthopedic Inst	531	500	12
9	Koh YG	20	Yonsei Sarang Hosp	1711	1640	14
10	Maffulli N	20	University of Salerno	526	501	12

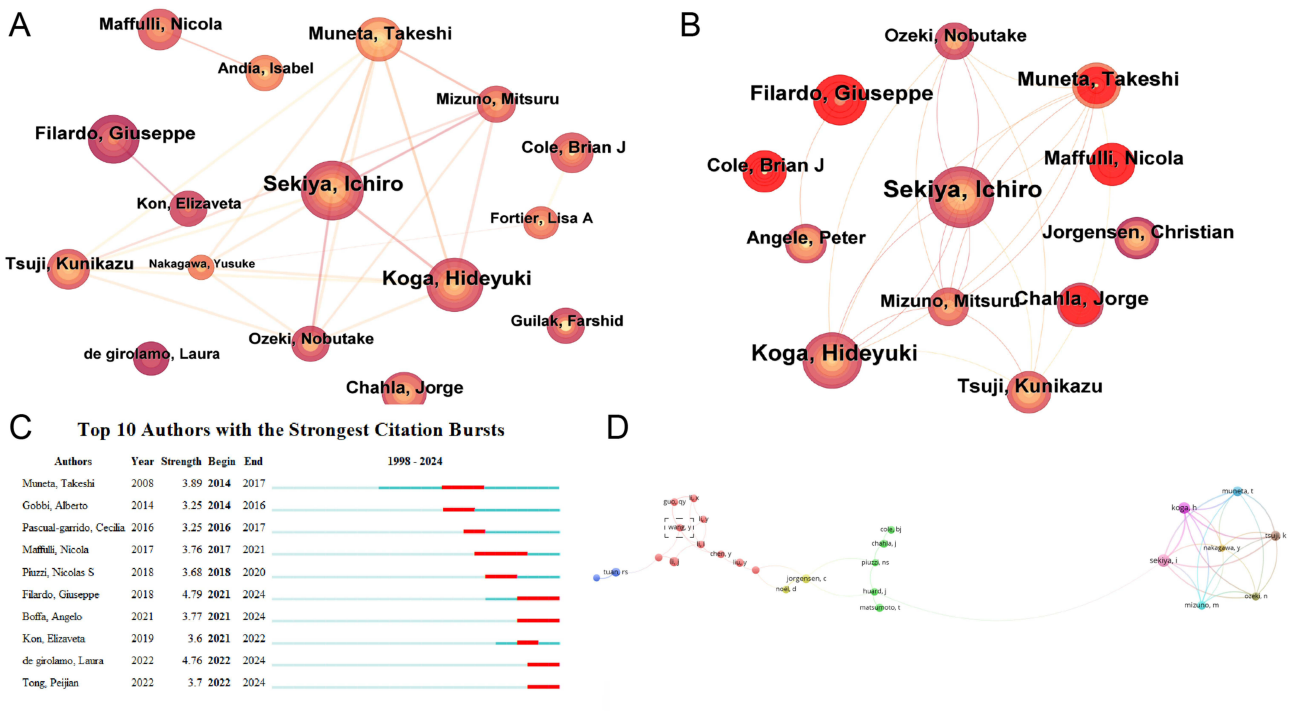

Figure 4 Co-occurrence analysis of authors. (**A**) The 16 authors with the most cooccurrences. (**B**) The top 12 authors ranked by centrality. (**C**) Author appearances; red represents appearances, dark green represents the years in which the author appeared, and light green represents the author's nonappearance. (**D**) Collaboration map between authors. The larger the circle is, the more papers the author has published and the more connections and collaborations he has with other authors.

collaborated with each other (Figure 4D). Sekiya I[13–15] is the most active collaborator (7 links; total link strength 128), followed by Koga H[16,17] (6 links; total link strength 120) and Tsuji K[18] (6 links; total link strength 97). Wang Y[19,20] has only 16 articles, but he is also actively seeking collaboration with other authors. Although Wang y has only 16 posts, he is also actively seeking collaboration with other authors, and there may be a trend of explosive growth in the number of posts. Authors with a greater volume of publications will be more active in seeking mutual collaboration with other authors.

Bibliometric Analysis of Keyword Co-Occurrence

Keywords serve as a highly condensed version of the article's topic, and research directions or highlights can be identified through co-occurrence analysis.[21] In the co-occurrence network visualization of the topic terms (Figure 5A), the red clusters represent basic research on stem cell therapy for OA, and the green clusters represent clinical research. Research frontiers in the field were captured through Citespace and VOSviewer keyword clustering, with the following identified terms: "High tibial" (Cluster 0), "Subchondral bone" (Cluster 1), "Platelet-rich plasma" (Cluster 2), "Mesenchymal stem cells" (Cluster 3), "Cell therapy" (Cluster 4), "Oxidative stress" (Cluster 5), "Stem cells" (Cluster 6), "Tissue engineering" (Cluster 7), "Stem cells" (Cluster 8), "Synovial fluid" (Cluster 9), and "Extracellular vesicles" (Cluster 10) (Figure 5B). VOSviewer was used on the basis of the average publication year (blue: earlier; red: later) (Figure 5C). In total, we obtained 71 keywords with at least 59 occurrences. The 5 most frequent keywords were "Osteoarthritis" (total link strength: 7273), "Mesenchymal stem cells" (total link strength: 4667), "Knee osteoarthritis" (total link strength: 4213), "Repair" (total link strength: 2525), and "Platelet-rich plasma" (total link strength: 2187). Most of these keywords appeared before 2020, while relatively new keywords appearing between 2021 and 2024 included "exosomes" and "extracellular vesicles". The following 10 main clusters were identified via CiteSpace: "High tibial" (Cluster 0), "Subchondral bone" (Cluster 1), "Platelet-rich plasma" (Cluster 2), "Mesenchymal stem cells" (Cluster 3), "Cell therapy" (Cluster 4), "Oxidative stress" (Cluster 5), "Stem cells" (Cluster 6), "Tissue engineering" (Cluster 7), "Stem cells" (Cluster 8), "Synovial fluid" (Cluster 9),

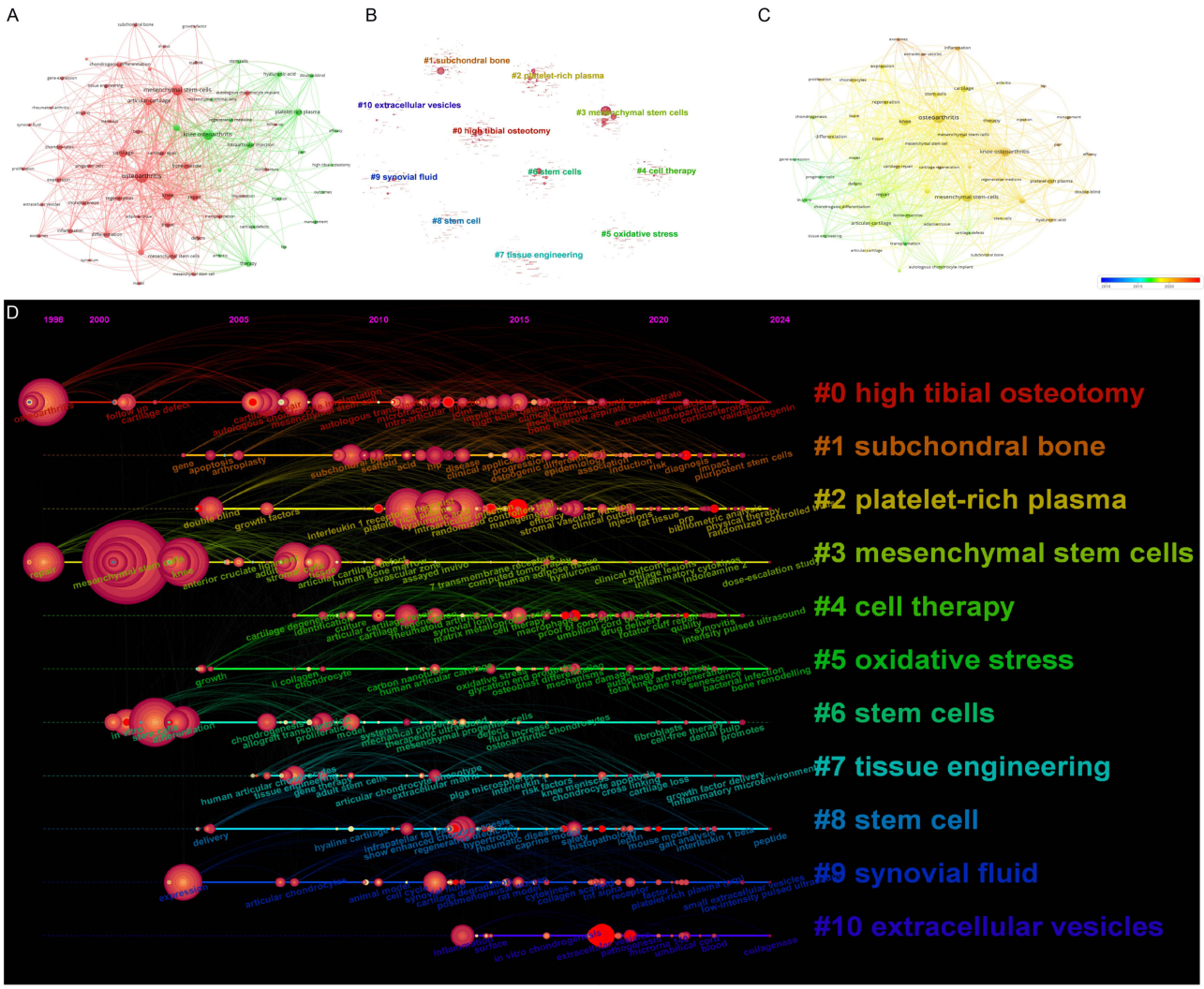

Figure 5 Keyword mapping for stem cell therapy for osteoarthritis. (**A**) The red cluster represents basic research, and the green cluster represents clinical research. (**B**) Keywords generated by VOSviewer are distributed according to the average publication year (blue: earlier; red: later). (**C**) Keyword cluster analysis mapping, where keywords from similar studies are grouped into clusters and one color represents a cluster. (**D**) Timeline of keywords generated by CiteSpace from 1998 to 2024.

and ”Extracellular vesicles” (Cluster 10) (Figure 5D). Clusters 0 and 3 are the earliest research hotspots; Clusters 2, 5, 6, and 8 are midterm research hotspots; and Clusters 7 and 10 are current research hotspots. The CiteSpace algorithm was used to investigate keyword bursts and reveal the 10 keywords with the strongest citation bursts (Figure 6). The keywords with the strongest citation explosions are ”Extracellular vesicles” (strength = 15.03), ”Repair” (strength = 12.81), and ”Transplantation” (strength = 12.57). Extracellular vesicles ”, ”Exosome”, and ”Pain” are the most cited in the recent outbreak of 2021–2024, indicating that these topics are the most cited in recent research; these topics are likely to be the next potential future research topics.

Distribution of Countries/Regions and Institutions Contributing to the Field

A total of 82 countries/regions have published research in this field, and the top 10 countries in terms of number of publications, number of collaborations, and centrality are listed in Table 4. The top three countries/regions in terms of the number of cooccurrences are the People’s Republic of China, the United States, and Italy (Figure 7A). The top three countries/regions in terms of centrality are the United States, England, and India (Figure 7B). In terms of the highest citation strength, Japan had the highest citation strength of 10.36 from 2001 to 2009, whereas Canada ranked 2nd with a strength of 10.04 from 2007 to 2013. In the past 2–3 years, the citation strength of Russia and India has been gradually

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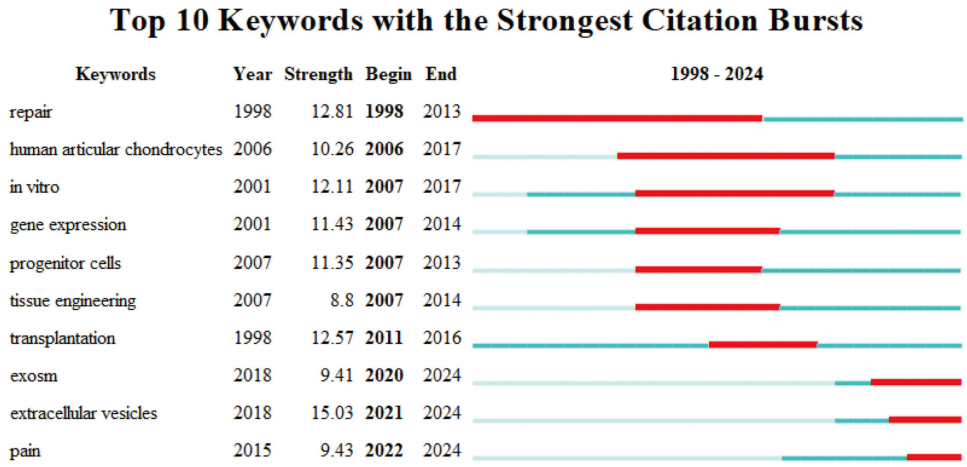

Figure 6 Keyword emergence: red represents emergence, dark green represents the year in which the keyword appeared, and light green indicates that the keyword did not appear.

increasing, indicating that the interest of these two countries in stem cell therapy for OA has increased (Figure 7C). From the perspective of national collaboration, the United States is most focused on seeking collaboration, and the People's Republic of China is the most important partner of the United States, followed by Japan and Germany (Figure 7D).

A total of 2875 institutions have published relevant literature in this area over the past 26 years. The largest subnetwork of interinstitutional collaborations is shown in Figure 8. Table 5 lists the top 10 institutions in terms of the number of publications, number of collaborations and centrality. The top three institutions with the highest number of cooccurrences are the University of California system, Institut National De La Sante Et De La Recherche Medicale (INSERM), and Tokyo Medical Dental University (Tmdu) (Figure 8A). The top three institutions in terms of centrality are the Institut Nationa. De La Sante Et De La Recherche Medicale (INSERM), University of California system, and Kyoto University (Figure 8B). As shown in Figure 8C, 10 organizations were analyzed for burst strength, and the top three organizations were the IRCCS Istituto Ortopedico Rizzoli, with a strength of 6.36 and an outbreak from 2009–2017. For Radboud University Nijmegen, the strength was 6.07, and an outbreak occurred from 2006–2015. The strength of the Royal National Orthopedic Hospital NHS Trust was 5.17, and an outbreak occurred from 2012–2013. The top three most collaborative institutions are Shanghai Jiao Tong University (10 links; total link strength: 30), the Chinese University of Hong Kong (12 links; total link strength: 29), and Queen Mary University London (4 links; total link strength: 28). Each top organization has established extensive links with other institutions (Figure 8D).

Table 4 Top 10 Most Productive Countries/Regions That Contributed Publications on Stem Cells for Osteoarthritis

Rank	Country/Region	Article Count	Percentage (%, N/2341)	Citation	Average Citation
1	People's Republic of China	640	27.339%	17,870	27.92
2	USA	624	26.655%	28,562	45.77
3	Italy	174	7.433%	6004	34.51
4	Japan	161	6.877%	6365	39.53
5	South Korea	149	6.365%	7700	51.68
6	Germany	148	6.322%	5379	36.34
7	England	147	6.279%	5375	36.56
8	Netherlands	90	3.845%	5789	64.32
9	Spain	87	3.716%	3445	39.6
10	Australia	79	3.375%	3195	40.44

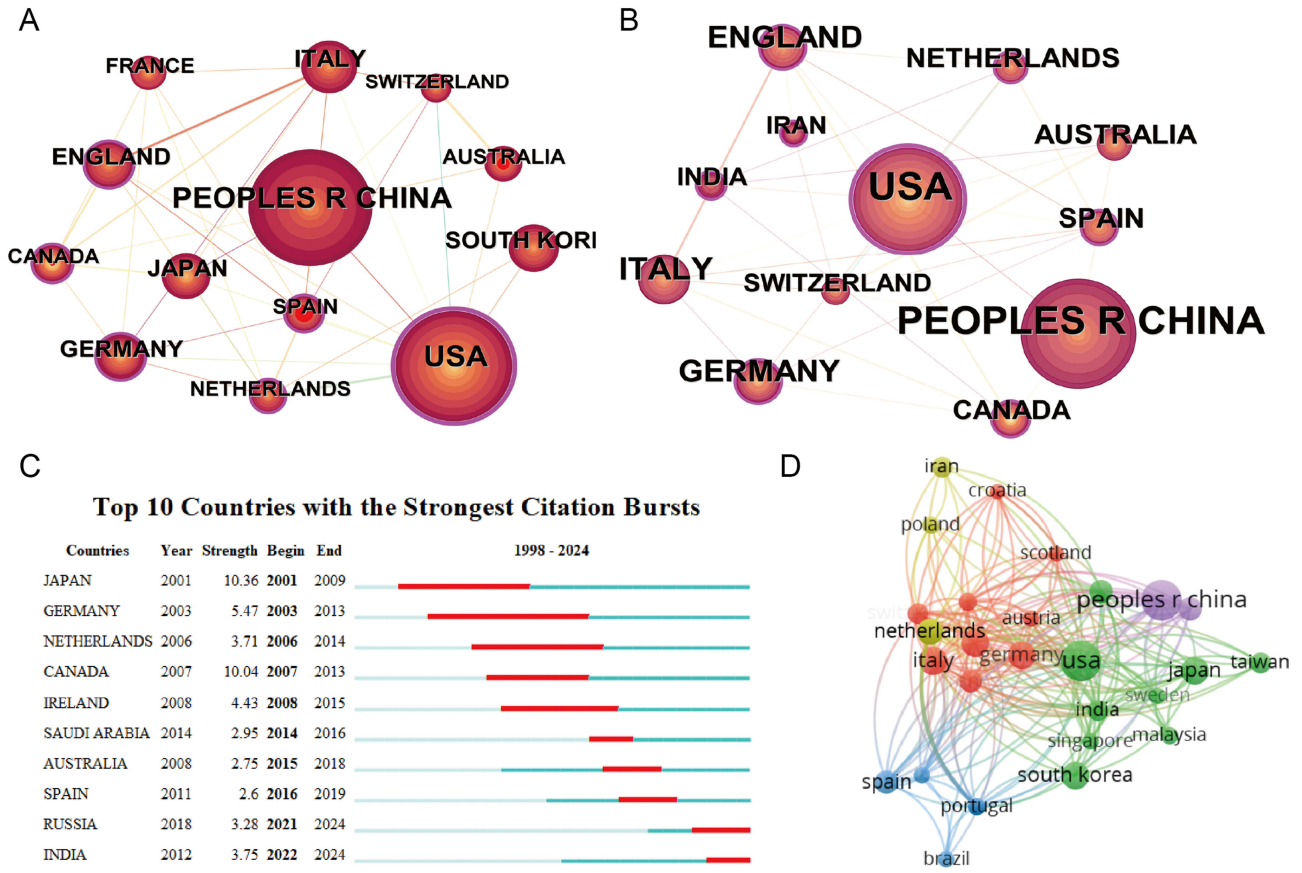

Figure 7 Co-occurrence analysis of countries/regions. (**A**) The 13 countries with the most cooccurrences. (**B**) The top 12 countries ranked by centrality. (**C**) Country appearance; red represents appearance, dark green represents the year the country appeared, and light green indicates that the country did not appear. (**D**) A map of previous collaborations between countries. The larger the circle is, the more papers the country has published and the more connections and collaborations it has with other countries.

Discussion

There are many studies on stem cell therapy for OA that provide a solid foundation for clinical translation. However, these studies are relatively scattered, fragmented, and subjective.[22] A comprehensive assessment of this research is needed to understand the research priorities in the field and to predict future trajectories.

Previous studies have analyzed the literature from 2001 to 2021 and concluded that the United States led the field, with Tokyo Medical and Dental University and Sekiya Ichiro as the first institution and first author in the field, respectively. Institutions and researchers from the United States, China, and Japan contributed the most to the field. Stem cell therapy for OA is a promising field.[9]

This work aimed to explore research prospects in specific areas by applying visualization techniques and network-related technologies. By using these methods, we can provide researchers with a brief overview of the current research status, make predictions about the research frontiers, and lay a more solid foundation for the development of OA treatment.

Publication Outputs

This paper presents an intuitive and effective systematic analysis of relevant literature in the field of stem cell therapy for OA by using CiteSpace and VOSviewer software. Knowledge mapping was used to show the collaborations of countries/institutions, research topics of interest, etc., and revealed the current status of research and future development trends in this field; this information can guide the development of this field.[11] The number of published papers represents, to a certain extent, the degree of importance attached to this research field by academics.[23] According to the trends in paper

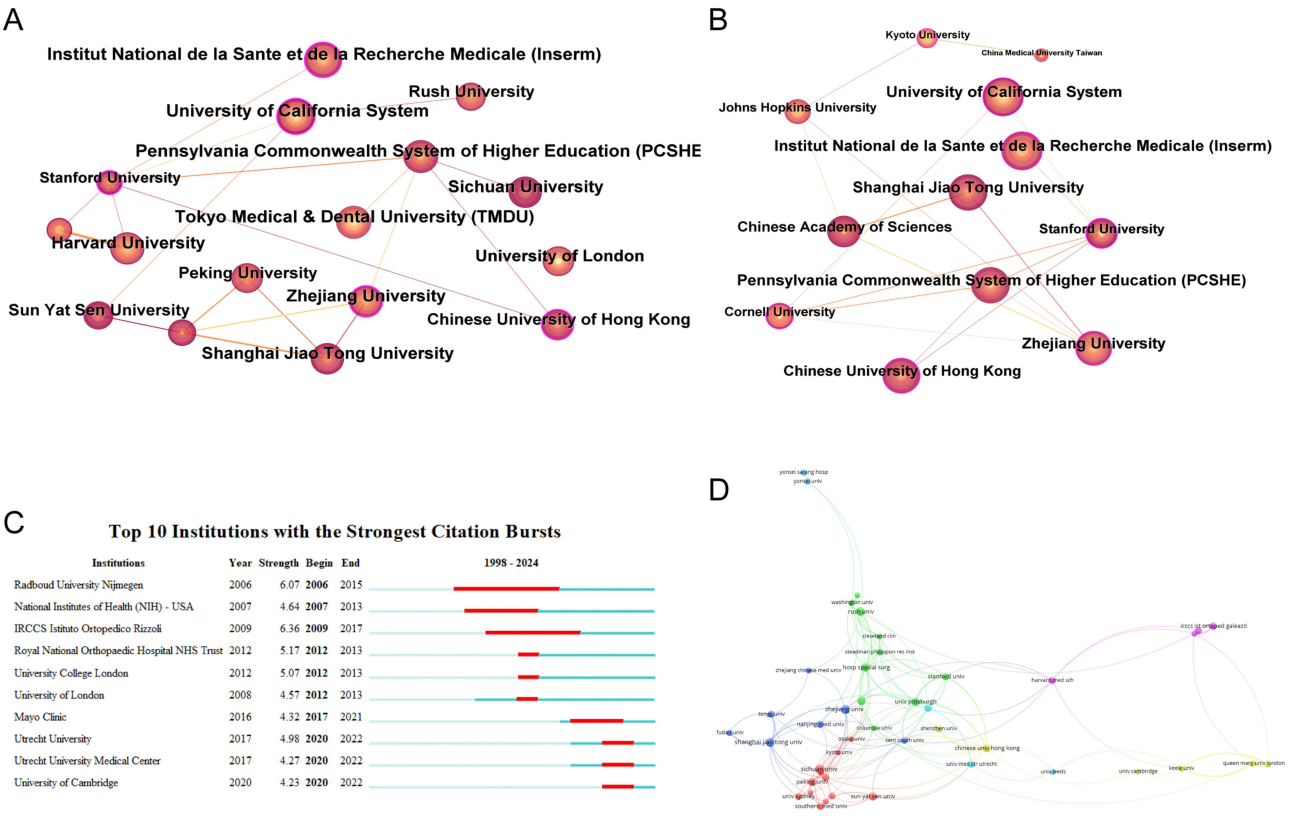

Figure 8 Co-occurrence analysis of institutions. (**A**) The 16 institutions with the most cooccurrences. (**B**) The top 12 institutions ranked by centrality. (**C**) Author appearances; red represents appearances, dark green represents the years in which the institution appeared, and light green indicates years in which the institution did not appear. (**D**) Collaboration map between institutions. The larger the circle is, the more papers the institution has published and the more connections and collaborations it has with other institutions.

publication, the number of articles on stem cell therapy for OA has been increasing annually, and the period can be roughly divided into two phases: from 1998–2017, the development of the field was relatively slow, and the development of the field was faster from 2018–2024. Therefore, stem cell therapy for OA is attracting increasing attention, and more in-depth research on this topic is needed. From 1998 to the present, a total of 2341 articles have been published in 513 journals. These journals provide good platforms for research and academic communication on stem cell therapy for OA.

Table 5 Top 10 Institutions That Contributed Publications on Stem Cells for Osteoarthritis

Rank	Institution	Country	Article Count	Percentage (%, N/2341)	Total Citation	Average Citation
1	University Of California System	USA	50	2.136%	3652	73.04
2	Institut NationaL De La Sante Et De La Recherche Medicale Inserm	France	46	1.965%	2532	55.04
3	Tokyo Medical Dental University Tmdu	Japan	44	1.880%	1901	43.2
4	Pennsylvania Commonwealth System Of Higher Education Pcshe	USA	43	1.837%	2130	49.53
5	Harvard University	USA	42	1.794%	2136	50.86
6	Sichuan University	China	42	1.794%	1438	33.76
7	ZheJiang University	China	41	1.751%	2240	54.63
8	Shanghai Jiao Tong University	China	40	1.709%	2149	53.73
9	University Of London	UK	40	1.709%	1376	34.4
10	Rush University	USA	37	1.581%	2013	54.41

Osteoarthritis and Cartilage has the greatest number of published articles, which suggests that this journal may become an important source of future research on stem cell therapy for OA, and more attention should be given to this topic.

Scientific Collaboration Network Analysis

Analyzing the collaborations between countries, institutions and authors can not only reveal the number of publications but also intuitively reflect their connections, the status quo and development in the entire field, further revealing the structure and evolution of the discipline and providing references for the occurrence and development of OA stem cell therapy. Such an analysis could also help researchers use existing resources more efficiently.[11] The top 10 countries are located in North America (USA), Asia (People's Republic of China, Japan, South Korea, and Australia), and Europe (Germany, England, Italy, the Netherlands, and Spain). Four of the top 10 authors are from Japan, and four are from Italy; all four Japanese authors are from Tokyo Medical and Dental University, suggesting that this institution is a precipitous leader in research on stem cell therapy for OA in Japan. The three institutions with the most publications were the University of California system, Institut National De La Sante Et De La Recherche Medicale (INSERM), and Tokyo Medical Dental University (TMDU). The top ten authors and their institutions are the major research forces in the field. China has the highest number of publications, and the overall performance of Chinese institutions and authors is good, which may be related to the collaborations between institutions and authors as well as the substantial funding of the National Natural Science Foundation of China (NSFC) in this field. Prof. Sekiya I[13–15] has published several important papers exploring the molecular mechanisms of stem cell therapy for OA and the potential of induced pluripotent stem cells as a therapeutic approach. These studies have played important roles in the development of stem cell therapy for OA. Kon E,[24] De Girolamo L[24] and Maffulli N[25] focused more on injecting biologics and observing their clinical efficacy. In summary, although stem cell therapy for OA has been a popular research topic among countries, institutions and authors, cooperation and communication between different research institutions and teams still need to be strengthened.

Current Research Focus

Hot spots and frontiers in a field have always been a popular topic in academia because they represent the most concentrated research efforts in a particular field and the latest trends in that field.[26] The key words of an article are usually highly condensed and concentrated summaries of the main points of the article, and if the frequency of a keyword is high, it is regarded as a research hotspot. Keyword co-occurrence analysis revealed that "exosome", "extracellular vesicles", "transplantation", and "tissue engineering" were the most important keywords in this field in the last decade. Recently, researchers have shown that inhibiting inflammation and stem cell differentiation are important mechanisms by which stem cells repair damage induced by OA.[27]

There has also been a dramatic increase in the use of the keyword "tissue engineering", suggesting that translational medicine research in stem cell therapy for OA involves not only simple stem cells that can treat OA but also methods to increase the number of remaining stem cells in the injured area. Currently, the graft materials used for osteochondral grafting to produce biological articular cartilage surfaces include the periosteum, chondrocyte membranes, osteochondral bone, allografts, and glucose membranes and collagen gels containing chondrocytes.[28] Tissue engineering strategies can optimize the combination of seed cells, scaffolding materials and bioactive factors according to the specific requirements of OA treatment to significantly complex microenvironmental changes that occur after osteoarthritis and induce endogenous/exogenous neural stem cells to differentiate into functional cells, which can remodel the microenvironment and ultimately restore motor function.[29] The use of biomaterials in combination with cytokines or stem cells can reduce the size of the injured area and restore motor function.[30]

Exosomes are rich in proteins, lipids, and nucleic acids (DNA, mRNA, miRNA, lncRNA, and tRNA) that can be delivered to receptor cells and affect their gene expression through multiple pathways.[31] By translating specific functional proteins or inhibiting the expression of specific functional genes, exosomes can regulate cellular functions and promote or ameliorate the development of diseases.[32] Many clinical studies have shown that exosomes can regulate the physiological functions of chondrocytes, maintain cellular homeostasis, and inhibit the progression of apoptosis by participating in the information transfer between chondrocytes.[33] Compared with stem cells, exosomes have a longer

in vivo survival time, lower carcinogenicity, and higher delivery efficiency.[34] Exosomes cannot replicate in vivo and rapidly disintegrate after drug release; therefore, treatment with exosomes is unlikely to result in tumor formation or progression to malignancy.[35] Exosomes include oxidized nanoparticles that are accurately targeted to the desired region via the guidance of a magnetic field, greatly enhancing their targeting ability.[36] The use of exosomes as therapeutic agents and drug carriers offers new directions for the treatment of OA.

Research Frontiers

The mechanism of action of mesenchymal stem cell-derived exosomes (MSC-Exos) in the treatment of OA and cartilage injury is as follows:[1] promote the anabolism of the cartilage extracellular matrix and inhibit its catabolism;[2] promote the proliferation and migration of chondrocytes and inhibit their apoptosis;[3] promote energy balance in chondrocytes by restoring mitochondrial function; and[4] inhibit the inflammatory response and promote cartilage repair by regulating the polarization of macrophages.[37] There is increasing evidence that stem cells exert their therapeutic effects through paracrine mechanisms, primarily through the function of extracellular vesicles (such as exosomes).[38] Synovial-derived MSCs (SMSCs) have strong differentiation potential, and their paracrine exosomes play crucial roles in cartilage repair.[39] SMCSS-derived exosomes (SMSC-Exos) were injected into the joint cavity of collagenase-induced OA (CIOA) mice. The results showed that SMSC-Exos alleviated the degree of cartilage injury in the OA mouse model by promoting the proliferation and migration of chondrocytes. Exosomes extracted from fibroblast-like synovial cells can improve the activity and migration ability of chondrocytes and delay the degradation of the extracellular matrix. The underlying mechanism of action may be related to the regulation of the miR-106b-5p/TIMP2 pathway by the exosomal lncRNA H19.[40]

ADMSC-Derived Exosomes Inhibit the Inflammatory Response After OA

Studies suggest that ADMSC-derived exosomes (ASC-Exos) inhibit the expression of inflammatory cytokines and exhibit strong cartilage repair capacity after intervention. Tofiño-Vian M[41] reported that ASC-Exos prevented the aging of OA osteoblasts by alleviating oxidative stress and inhibiting inflammation. In an in vitro inflammation model, ASC-Exos reduced the production of the inflammatory mediators IL-6 and prostaglandin E2 by inhibiting β-galactosidase activity. These findings suggest that exosomes may alleviate OA through antiaging effects. Ragni[42] reported that ASC-EVs inhibited the expression of proinflammatory cytokines and chemokines in fibroblast-like synoviocytes in OA. In mouse models of medial meniscus (DMM) instability, exosomes alleviate OA progression and gait dysfunction by maintaining chondrocyte homeostasis.

IMSC-Exos Promote Chondrocyte Proliferation and Migration

Induced pluripotent stem cells (IMSCs) are widely available and have unlimited proliferation and differentiation capabilities, showing great potential for application in cartilage regeneration.[43] Zhu et al[44] compared the therapeutic effects of exosomes derived from IMSCs and SMSCs (IMSC-Exos and SMSC-Exos) on OA. In in vitro experiments, IMSC-Exos showed a stronger ability to promote chondrocyte proliferation and migration. In a collagenase-induced OA (CIOA) mouse model, although SMSC-Exos could reduce cartilage damage, the surface hyaline cartilage was replaced by fibrocartilage, resulting in the formation of irregular scars on the cartilage surface, whereas IMSC-Exos could completely repair cartilage damage.

Yan et al[45] reported that UMSC-derived exosomes (UMSC-Exos) promoted chondrocyte proliferation and migration and extracellular matrix synthesis and inhibited cell apoptosis by activating the transforming growth factor β1 (TGFβ1) and Smad 2/3 signaling pathways. They also reported that the number of exosomes produced by UMSCs in three-dimensional (3-D) culture was 7.5 times greater than that produced by UMSCs in two-dimensional (2-D) culture, which promoted cell proliferation and inhibited apoptosis.

Zavatti et al[46] reported that amniotic fluid stem cell-derived exosomes (AFCS-Exos) can induce THP-1 cells to transform into M2 macrophages in vitro; increase the expression of the anti-inflammatory factors IL-10 and TGF-β1; and reduce the expression of the proinflammatory factors IL-1β, IL-6, TNF-α, and IL-12. In an iodoacetic acid-induced OA rat model, AFCS-Exos repaired cartilage damage by promoting the polarization of M2 macrophages.

Highlights and Limitations

In this study, a bibliometric analysis of the literature on stem cell therapy for OA retrieved from the WoS core database from 1998 to 2024 was conducted to maintain objectivity and comprehensiveness in data analysis. This study provides a large amount of information to illustrate the current status, hot spots and prospects of stem cell therapy in OA research. In addition, to clearly present the bibliometric results, two visualization tools were combined. However, limitations inevitably occur. First, only original articles were included in the analysis. Second, because some words appear in multiple expressions, they are evaluated multiple times. Finally, all database searches were completed within one day to avoid bias arising from updated publications. However, new data can also be lost, although their effect on citation frequency is negligible.

Conclusion

Stem cells play an important role in OA treatment, and the number of related research papers has been steadily increasing in recent years. China and the United States are the leading countries in this research field. Currently, extracellular vesicles, exosomes and tissue engineering are research hotspots in this field. With the development of new therapies involving stem cell transplantation, exosome stabilization has become an important trend for future clinical applications. Given that mesenchymal stem cells (MSCs) are a stem cell type that is currently attracting substantial attention, experimental and clinical studies should be conducted in the future to promote the clinical application of stem cells.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no conflicts of interest in this work.

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