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Development of mesenchymal stem cells: therapeutic effect and prospect for rheumatoid arthritis

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Abstract

Rheumatoid arthritis (RA) is a chronic systemic autoimmune disease, and it cannot be cured currently. Mesenchymal stem cells (MSCs), an emerging therapeutic method, have been applied to treat RA. It is essential to learn more about RA and MSCs. A total of 1,296 records were retrieved from the Web of Science. Then, Citespace and VOSviewer were used for the scientometric analysis of the data, including national distribution, institutional distribution, author distribution, journals, funding, and keywords. Our analysis presents basic information on the research into treating RA with MSCs, identifies research hotspots, and outlines clear research directions for interested researchers. At present, research on MSCs and RA focuses on the diversity of therapeutic effects, inflammatory mechanisms, molecular mechanisms of MSCs from different sources, and extracellular vesicles of MSCs on RA. Cutting-edge research in this field is booming, and this study will promote the development of the scientific research and clinical applications of MSCs in treating RA.

Keywords Rheumatoid arthritis, Mesenchymal stem cells, Development, Research hotspots, Weaknesses

Introduction

Rheumatoid arthritis (RA) is an inflammatory autoimmune disease that occurs in joints, cartilage, and other organ systems, and its pathogenesis has not been fully elucidated [1–3]. Globally, the incidence of RA is about 0.5%, with a disability rate of 70% after three years [4]. At present, the therapy of RA is primary to control the further deepening of inflammation and the commonly used drugs include nonsteroidal anti-inflammatory drugs, disease-modifying anti-rheumatic drugs, glucocorticoids, and biological agents [5, 6]. However, long-term use of these drugs often leads to gastrointestinal side effects.

Mesenchymal stem cells (MSCs) are a kind of cell clusters which characterized by strong differentiation ability, immunomodulation, and anti-inflammatory effects. MSCs mainly exist in bone marrow, umbilical cord, fat, and placenta have the potential ability in inhibiting pro-inflammatory cells of innate and adaptive immune system [7]. At the same time, MSCs have the tissue regeneration ability, mainly reflected in the differentiate into osteoblasts, adipocytes, and chondrocytes under the induction of different media [8]. MSCs also exhibit low immunogenicity characterized by the low expression of MHC class I molecules and the absence of MHC class II molecules and costimulatory molecules [9]. The unique immune regulatory properties of MSCs promote it to regulate the local microenvironment, thereby facilitate tissue repair and improvement [8]. In general, immune

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regulation, tissue regeneration, and low immunogenicity make MSCs become a promising therpy for the RA treatment [10, 11].

Bibliometrics is a research method that integrates mathematics, statistics, keyword analysis, and citation analysis. The purpose of bibliometrics is to analysis the relevant research literature within the target research field, and intuitively present the development status and future directions of the particular field [12, 13]. Up to now, a number of software tools, such as VOSviewer, Citespace, and Pajek et al., have been developed for bibliometrics [14, 15]. Citespace and VOSviewer are two of the most frequently used visual analysis tools, providing effective and intuitive data for readers to evaluate structured content and effective developments in the field of research [16, 17].

MSCs in the treatment of RA have some problems, such as lack of concentration of research and unclear hot spots. Therefore, combing the existing research results, analyzing the development status and trend, and exploring the latest research direction and hot spots of MSCs treatment for RA have become a vital basis for further study. Thus, the literature on MSCs treatment of RA was searched, classified, and sorted through the Web of science (WOS), and the literature data in the past 20 years were visually analyzed from the aspects of publication time, annual publication amount, publication country, research team, research content, and research hotspots [18, 19]. And Citespace and VOSviewer were applied to draw knowledge graphs in order to provide reference for future related research.

Methods

Data source and retrieval strategy

In order to clearly understand the research status and trend of MSCs in treating RA from all directions and angles, and obtain high-level core journal literature data, the econometric statistics takes WOS database, which is a literature retrieval resource library and regarded as a comprehensive academic data resource with high recognition in academic field and a wide range [20]. Retrieval method (Fig. 1A): The retrieval formula is TS = (Mesenchymal stem cells) AND TS = (Rheumatoid arthritis). The time span is from January 1, 2004 to July 1, 2024. The literature types are articles and review articles. The data collection date is July 13, 2024. Finally, according to the

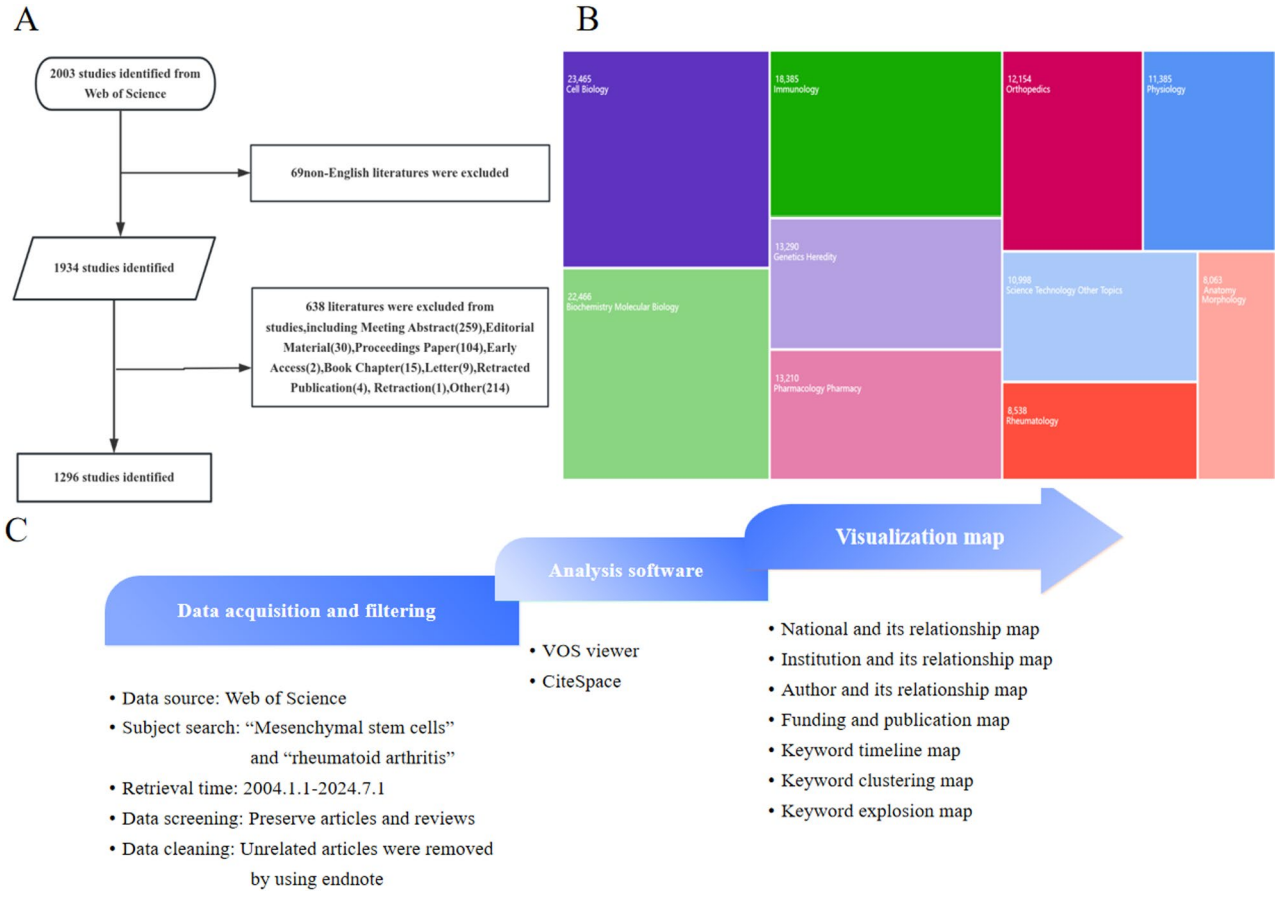

Fig. 1 Literature retrieval process and related fields. **A** Literature screening process the role of MSCs in the treatment of RA. **B** The role of MSCs in the treatment of RA is covered by the relevant literature. **C** Bibliometric analysis process of the role of MSCs in the treatment of RA

set conditions, a total of 2003 literatures were obtained. It involves cell biology, biochemistry molecular biology, immunology, genetics heritage, pharmacology pharmacy, orthopedics, science technology other topics, rheumatology, physiology, and anatomy (Fig. 1B). Excluding 69 non-English literatures, 1934 English literatures were obtained, including Meeting Abstract (number = 259), Editorial Material (number = 30), Proceedings Paper (number = 104), Early Access (number = 2), Book Chapter (number = 15), Letter (number = 9), Retarded Publication (number = 4), Retraction(number = 1), and other (number = 214). Preserve areticles (number = 987) and reviews (number = 309) are finally retained.

Data analysis and visualization

After eliminating 707 duplicate and irrelevant literatures, a total of 1296 effective literatures meeting the criteria were finally obtained, which constituted the basic data set of this study. Citespace is a software that can visually analyze the documents in most of the world's literature databases, such as China HowNet and WOS, and can help researchers to understand the development process of the research field and to better judge the future research hotspots. VOSviewer belongs to one of many scientific knowledge mapping softwares It realizes the mapping of scientific knowledge by constructing the relationship of "network data" and visual analysis, shows the relationship between the structure, process and cooperation in the research field, and helps researchers to understand the future trend of the research field in multiple dimensions [20, 21]. Among them, the time distribution map of literature output and the proportion of national publication volume were plotted by Excel software, while the national cooperation map, institutional cooperation map, author cooperation map and keyword co-occurrence map were drawn using VOSviewer and Citespace, the institutional publication volume was presented by Power Point (Fig. 1C).

Results

Analysis of the time characteristics and overall development trend of literature publication

The different growth rates of the number of published documents in different years can reflect the research popularity and development trend to a certain extent. The time distribution of the number of published literatures is shown in Fig. 2A. According to the data, the global literature output in 2004–2005 was all in the single digits, indicating that the research on MSCs treatment of RA had not attracted wide attention, and the research was in the initial stage of exploration. In 2006, the output of literature appeared in double digits for the first time, with 14 papers published. From 2006 to 2010, it entered a stage of rapid growth. From 2011 to 2024, it began to enter a stable growth stage and showed a continuous rising trend, reflecting the gradual attention and concern of the research value of MSCs in the treatment of RA.

Analysis on time characteristics and overall development trend of literature citation

The citation of documents in different years represents the current research enthusiasm of documents, and the citation of documents in different years reflects the mainstream direction of research to some extent. The time distribution of literature citation is shown in Fig. 2D. The data show that the number of citations in 2004–2005 is no more than 100 times, which indicates that MSCs have been applied to RA as a new treatment technology. From 2011 to 2024, the number of citations increased year by year, indicating that MSCs are playing an increasingly important role in the treatment of RA. Among the top 15 articles with the highest number of citations (Tables 1), Identification of Mesenchymal Progenitor Cells in Normal and Osteoarthritis Human Articular Cartilage was the earliest published article in the cited literature, and it was cited 13 times in the second year, indicating that mesenchymal stem cells have received great attention from researchers after being applied to rheumatoid arthritis. From 2011 to 2024, the direction of cited literature changed from the physiological characteristics of mesenchymal stem cells to the mechanism of mesenchymal stem cells treating rheumatoid arthritis. It shows that researchers have conducted extensive research on the application of MSCs in the treatment of RA.

Analysis of the country characteristics and cooperation network relationship of literature publication

Among countries and collaborative networks, a total of 77 countries have contributed to the literature production of MSCs for RA over the past 20 years (Fig. 2B). China has the largest number of papers, accounting for 412 papers, indicating that China's output in the field of MSCs treatment of RA occupies an absolute advantage and has an obvious dominant position. The top 10 countries with the most prominent contributions to the research of MSCs for RA treatment are China, United States of America, Germany, England, Japan, South Korea, Italy, France, Iran, and Spain (Fig. 2C). These countries also play a crucial role in the research in this field. The trend of publication in each country is basically the same, which reflects the global trend of publication in line with the results presented in Fig. 2A. In 2011, there was a temporary decline in the number of articles published by all countries.

At the same time, the VOSviewer (Fig. 2E) and Citespace (Fig. 2F) software were used to create a network map of national cooperation. VOSviewer parameters were set as follows: Method (Linlog/modularity)

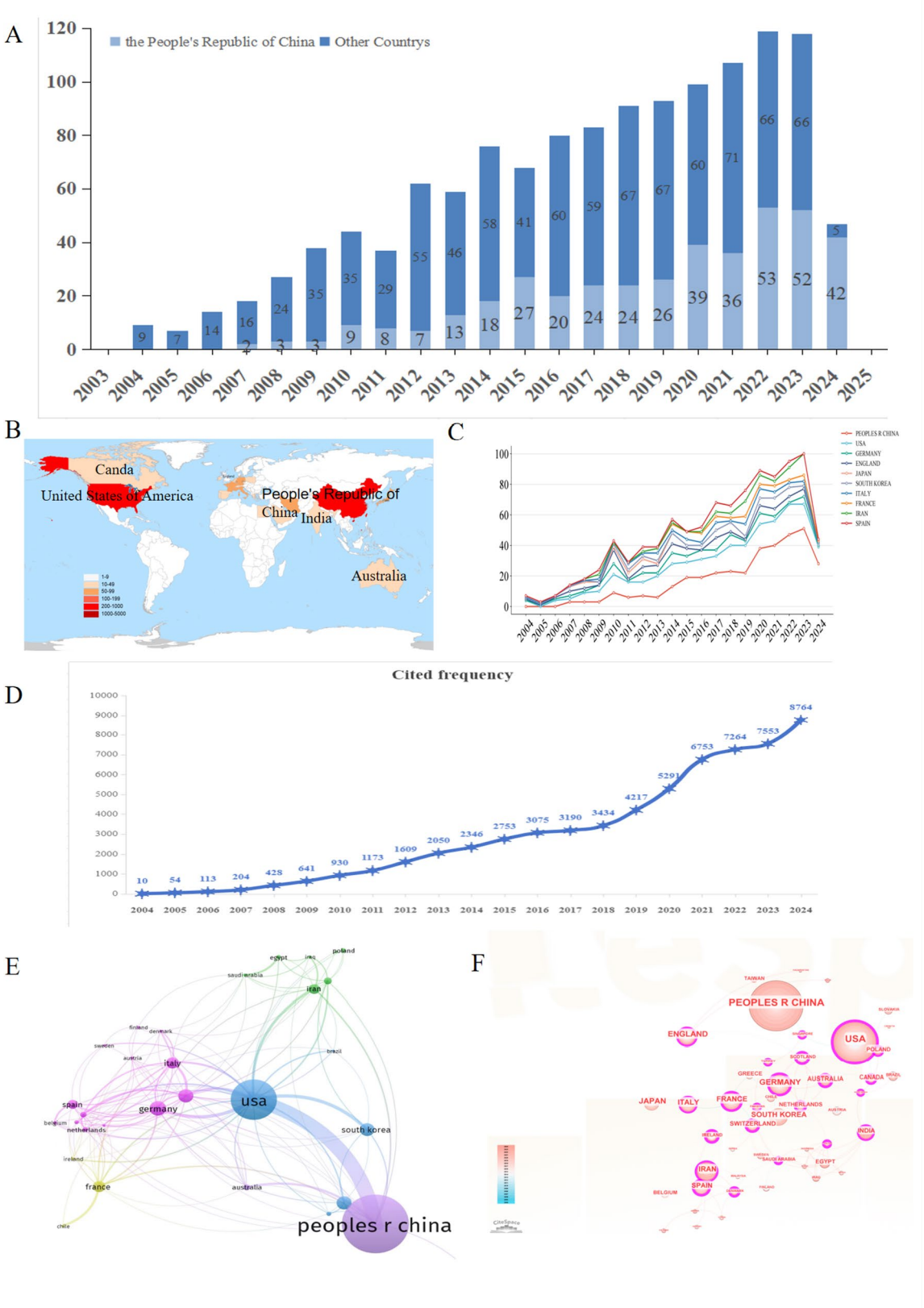

Fig. 2 Cooperation map of countries/regions in MSCs and RA. **A** Distribution map of the proportion of national documents issued. **B** Distribution map of annual publication volume between China and other countries. **C** Annual number of publications in the top 10 countries. **D** Citation of annual documents. **E** Visualization of countries/regions by VOSviewer network. **F** Visualization of countries/regions by CiteSpace network

Table 1 The top 15 most cited documents

Title	Source title	Publication year	Total citations	Average per year
The role of synovitis in osteoarthritis pathogenesis	Bone	2012	1002	71.57
Mesenchymal Stem Cells: Mechanisms of Inflammation	Annual review of pathology: Mechanisms of diease	2011	762	50.8
Update on the Pathomechanism, Diagnosis, and Treatment Options for Rheumatoid Arthritis	Cells	2020	668	111.33
Cartilage homeostasis in health and rheumatic diseases	Arthritis research & Therapy	2009	661	38.88
Inflammatory Cytokine-Induced Intercellular Adhesion Molecule-1 and Vascular Cell Adhesion Molecule-1 in Mesenchymal Stem Cells Are Critical for Immunosuppression	Journal of Immunology	2010	578	36.13
Immunosuppressive Properties of Mesenchymal Stem Cells: Advances and Applications	Current molecular medicine	2012	577	41.21
Stromal Cell-Derived Factor 1/CXCR4 Signaling Is Critical for the Recruitment of Mesenchymal Stem Cells to the Fracture Site During Skeletal Repair in a Mouse Model	Arthritis and rheumatism	2009	560	32.94
Cell therapy using allogeneic bone marrow mesenchymal stem cells prevents tissue damage in collagen-induced arthritis	Arthritis and rheumatism	2007	549	28.89
Identification of mesenchymal progenitor cells in normal and osteoarthritic human articular cartilage	Arthritis and rheumatism	2004	480	21.82
Treatment of Experimental Arthritis by Inducing Immune Tolerance With Human Adipose-Derived Mesenchymal Stem Cells	Arthritis and rheumatism	2009	473	27.82
Interaction between bone and immune cells: Implications for postmenopausal osteoporosis	Seminars in cell & Development biology	2022	462	115.5
Mesenchymal stem cells-derived exosomes are more immunosuppressive than microparticles in inflammatory arthritis	Theranostics	2018	402	50.25
Intra-articular treatment options for knee osteoarthritis	Nature reviews rheumatology	2019	386	55.14
Human adipose-derived mesenchymal stem cells reduce inflammatory and T cell responses and induce regulatory T cells in vitro in rheumatoid arthritis	Annals of the rheumatic diseases	2010	377	23.56
Trafficking and Differentiation of Mesenchymal Stem Cells	Journal of cellular biochemistry	2009	362	21.29

and a minimum number of country documents: 20. The obtained results were retrieved from 77 countries. With each node representing a country and the size of the node proportional to the frequency of its appearance. The thickness of the lines connecting the nodes corresponds to the strength of the cooperation between the two countries. China has established cooperative relationships with the United States of America, Italy, Switzerland, Singapore, Japan, Australia, India, etc. Among them, China has the closest cooperation with the United States of America. The United States of America has established cooperative relations with Germany, South Africa, Iran, Italy, and Australia, among which China and Germany are the closest. CiteSpace parameters were set as follows: time slice (2004–2024), years per slice (1), term source (entire selection), node type (country), and selection criteria (top $N = 60$). Other parameters were left at the default settings. Nodes represent countries that occupy an important position in the research field, and Citespace directly reflects the national media centrality of the research field.China is by far the largest country in this field.The purple outer ring represents the medium centrality, which can reflect that the country has a reference status in the research field of MSCs treatment of RA. Several countries, such as the United States of America, the United Kingdom, Germany, Australia, France, Italy, and Spain, are of reference value.

Analysis of the institutions characteristics and the relationship of cooperation network of literature publication

The paper also analyzed the relevant research institutions and drew the maps by using VOSviewer (Fig. 3A) and citespace (Fig. 3B). A total of 1526 research institutions have conducted research on the treatment of RA with MSCs. VOSviewer parameters were set as follows: Method (Linlog/modularity) and a minimum number 3. The obtained results were retrieved from 235 institutions. In the figure, different colors represent different research directions among institutions, and the same color is used for institutions with similar or consistent research directions. The distribution of nine colors can be seen intuitively, and the color depth is consistent with the number of documents in the institution. By analyzing

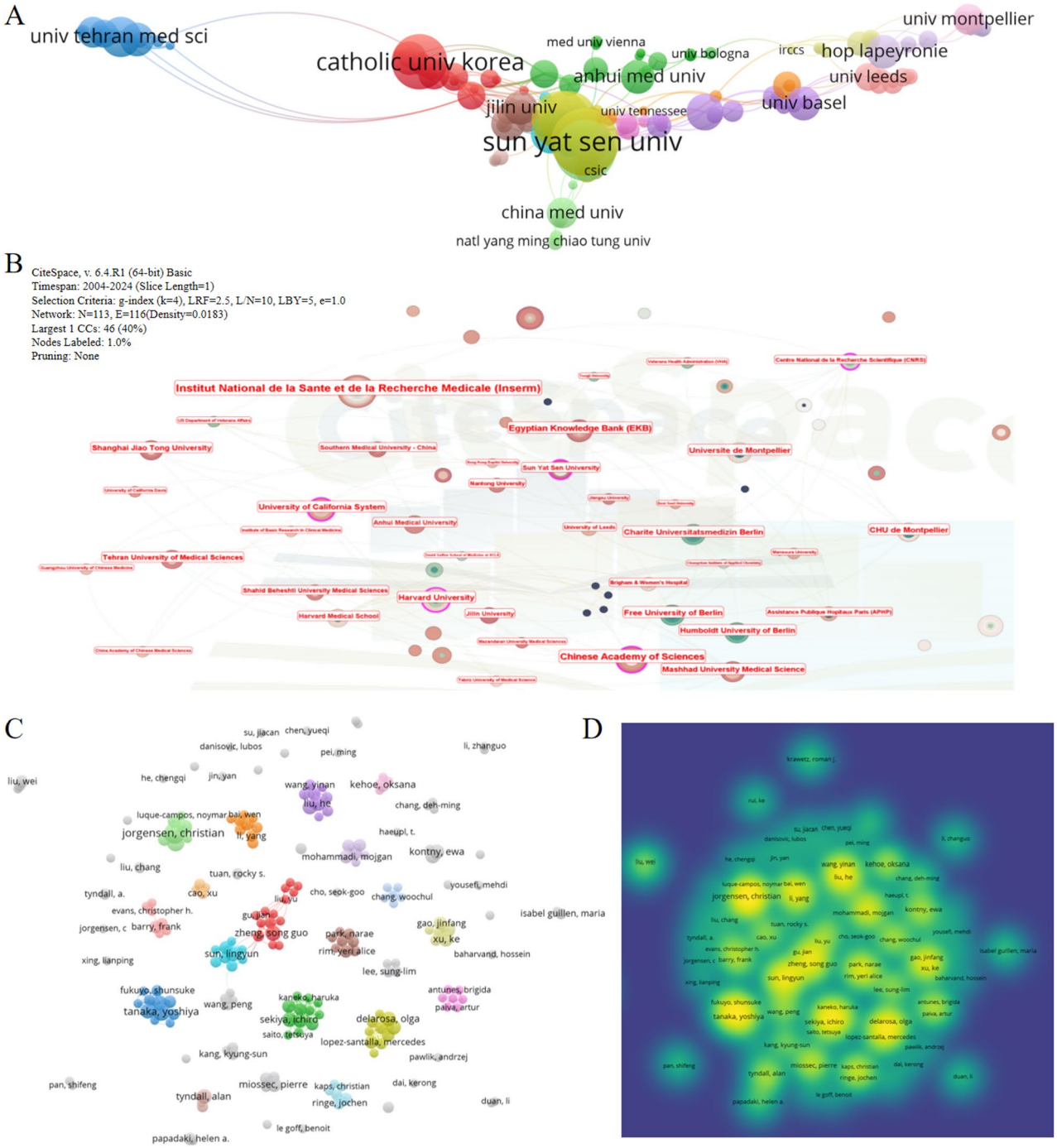

Fig. 3 Cooperation map of institutions and authors in MSCs and RA. **A** Visualization of institutions by VOSviewer network. **B** Visualization of institutions by CiteSpace network. **C** Authors collaboration network. **D** Density visualization map of co-cited authors

the document data, it is known that Sun Yat-sen University (number = 22), Sichuan University (number = 20), Chinese Academy of Sciences (number = 19), and Shanghai Jiao Tong University (number = 19) in China have the largest number of publications. Among other relevant research institutions outside of China, the Catholic University of Korea (number = 18), Tehran University of Medical Sciences (number = 13), and Shahid Beheshti University of Medical Sciences (number = 10) have relatively large numbers of publications. The size of the circle is proportional to the number of posts issued by the agency. As can be seen intuitively, the exchanges and cooperation between various institutions are not close. CiteSpace parameters were set as follows: time slice

(2004–2024), years per slice (number = 1), term source (entire selection), node type (institutions), and selection criteria (top $N = 60$). Other parameters were left at the default settings. Among the relevant research institutions, Sun Yat-sen University, Chinese Academy of Sciences, Harvard University and University of California System are four research institutions with a medium centrality. They have some experience in the research field of MSCs treatment of RA. The graph intuitively and clearly reflects that the connections among various institutions are not close, and an academic exchange circle with certain influence has not been formed yet. These four research institutions are expected to become an important bridge for exchanges and cooperation among various institutions.

Analysis of the author and author cooperation network relationship of literature publication

The author cooperation network relationship of the research on MSCs in the treatment of RA is shown in Fig. 3C. VOSviewer parameters were set as follows: Method (Linlog/modularity) and a minimum number of documents of an author: number = 3. The obtained results were retrieved for 216. The size of the dots and the thickness of the connecting lines are positively correlated with the literature publication volume of the researchers and the closeness of the cooperation relationship among the researchers. Moreover, the color change of the graph represents the different cooperation times of the researchers (Fig. 3D). Analyzing from the overall perspective, it is not difficult to find that in the research process of nearly 20 years, the research on MSCs in the treatment of RA is constantly forming research teams with an increasingly larger scale and a more and more mature scientific research system.At present, there are increasingly large research teams, but the cooperative relationship between the teams has not been formed, and the cooperation and communication have not been established. Professor Christian Jorgensen has published 14 articles with as many as 1,336 citations.Professor Daniele Noel has published 10 articles with 1,186 citations. This was followed by Li Yang, Bai Wen, Liu He, Wang Yinan, Mohammadi Mojgan, Kontmy, Liu Yu and Zheng Songguo.Professor Liu He from Guangzhou Regenerative Medicine and Health Guangdong Laboratory has published 7 related articles with 291 citations.

Analysis of the publication status of literature and journals

The finally included 1296 papers were published in 201 kinds of journals. Among them, International Journal of Molecular Sciences had as many as 42 publications. Followed by Frontiers in Immunology, Arthritis Research Therapy, Stem Cell Research Therapy, Journal of Immunology, Arthritis and Rheumatism, Rheumatology Oxford England. The number of papers published in 10 magazines was all more than 20 (Fig. 4A), accounting for 16.12% of the total number of publications. 24 journals included 10 or more papers. Up to now, the treatment of RA by MSCs is in a rapid development stage. Compared with other fields, the amount of articles published in various journals is at a low level. It involves cell biology, biochemistry molecular biology, immunology, genetics heritage, pharmacology pharmacy, orthopedics, science technology other topics, rheumatology, physiology, anatomy.It provides reference data for the later publication, search, and reference of related research on MSCs in the treatment of RA.

Analysis of the sources of literature fund projects

Most of the retrieved literature had fund support. There were 201 funds in total. The top ten fund projects ranked by the number of publications among the literature with fund support are National Natural Science Foundation of China, National Institutes of Health United States Department of Health and Human Services National Institute of Arthritis, Musculoskeletal and Skin Diseases, NIH European Union Ministry of Education, Culture, Sports, Science and Technology of Japan UK Research and Innovation National Key R & D Program of China National Research Foundation of Korea (Fig. 4B). Through the data, it can be seen that the projects and topics supported by the National Natural Science Foundation of China have the largest number of published literatures. The top 10 ranked fund supports cover the highest fund supports of many countries such as the United States of America, the European Union, Japan, the United Kingdom, South Korea, and Germany, which also indicates that the research on MSCs in the treatment of RA has attracted increasing attention and emphasis from various countries.

The double map superposition of journals intuitively shows the distribution of topics covered by MSCs in the treatment of RA (Fig. 4C). The picture on the left shows the cited journals, and the other shows the cited journals. Labels represent academic fields covered by journals, and connecting lines represent citation relationships. The light in the picture clearly shows two main paths. The yellow citation path shows that the exploration of Molecular, Biology and Immunology is often cited by Molecular, Biology and Genetics journals. Green medical path shows that the research of Medicine, medical and Clinical is often cited by biology, Genetics journals and health, nursing and medical journals, and by Molecular, Biology and genetics journals.

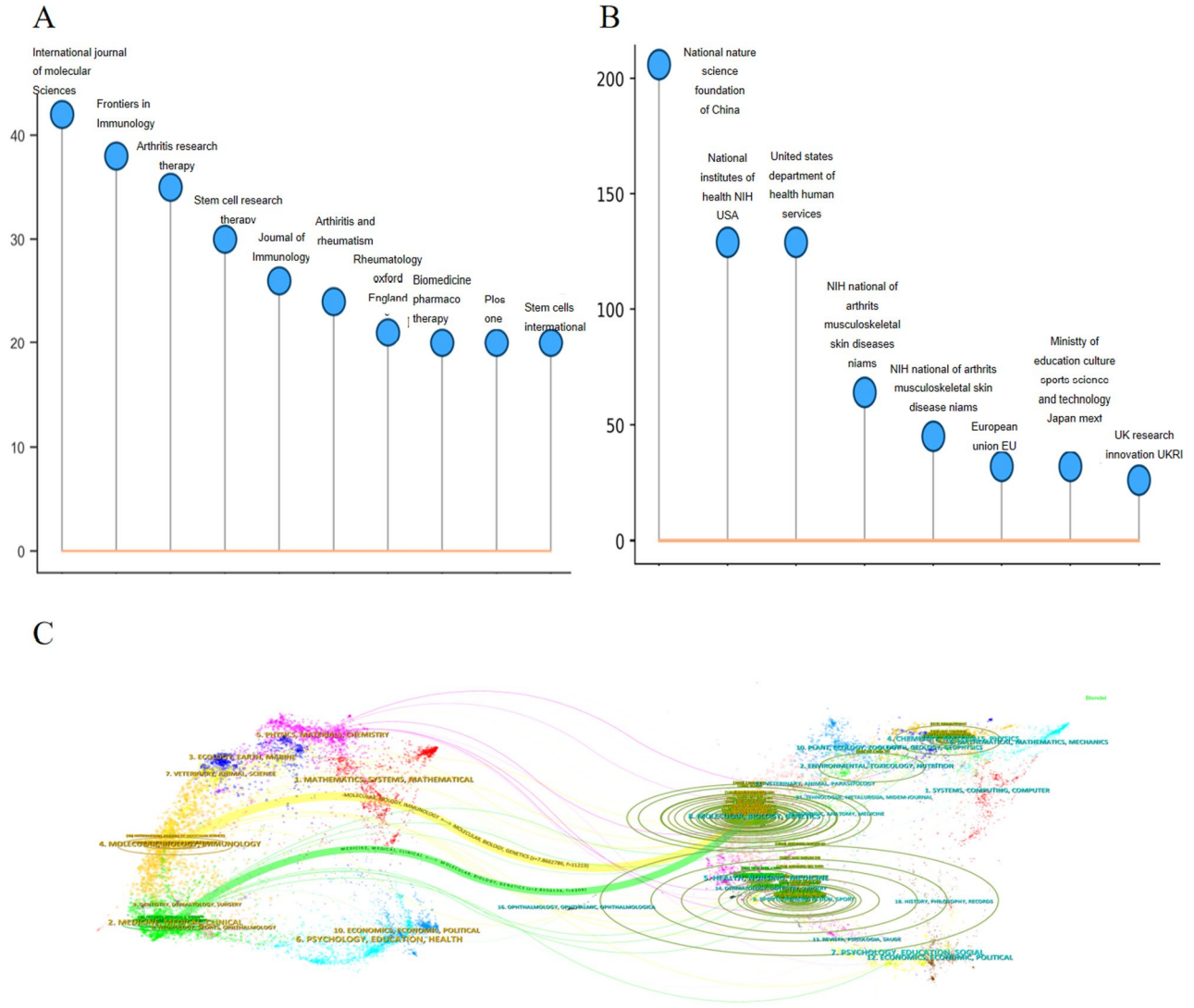

Fig. 4 Map of published journals and funds. **A** Publication of literature journals. **B** Documentation Fund project sources. **C** The dual-map overlay of journals

Analysis of the keyword hotspot

Keyword emergence analysis

Keyword emergence is to highlights the keywords that appear and use frequently in a specific period of time, which can reflect the changing trend of keyword frequency in effective literature, further reflect the forward-looking problems in this research field [22]. The appearance of different keywords also helps researchers to analyze and judge the research direction, research hotspots and current dynamic evolution trends in this field. In the past 20 years, a total of 4412 explosive keywords have been generated in the research of MSCs for the treatment of RA, covering multiple levels of research from active substances to experimental efficacy. The list of the top 25 keywords with the highest citation frequency is shown in Fig. 5A. The figure clearly and intuitively presents the distribution of research years of these keywords. Meanwhile, the hotspot strength represents the frequency of occurrence of the keyword within its research years. It can be roughly divided into three stages. From 2004 to 2014, researchers focused on MSCs themselves. In this stage, although it was in the trigger period of stem cell interest and the output of literature was relatively low, there were 13 burst terms emerging. It shows that in the initial exploration stage of MSCs in the treatment of RA, different researchers explored at different levels, and the research content was extensive and diversified. From 2014 to 2019, with the continuous improvement of research level and the deepening of research level, researchers conducted research on the mechanism of mesenchymal stem cell therapy for RA. However, there were only five burst terms during these five years. It is related to the standardized management of the application of stem cells and the release of relevant policies and

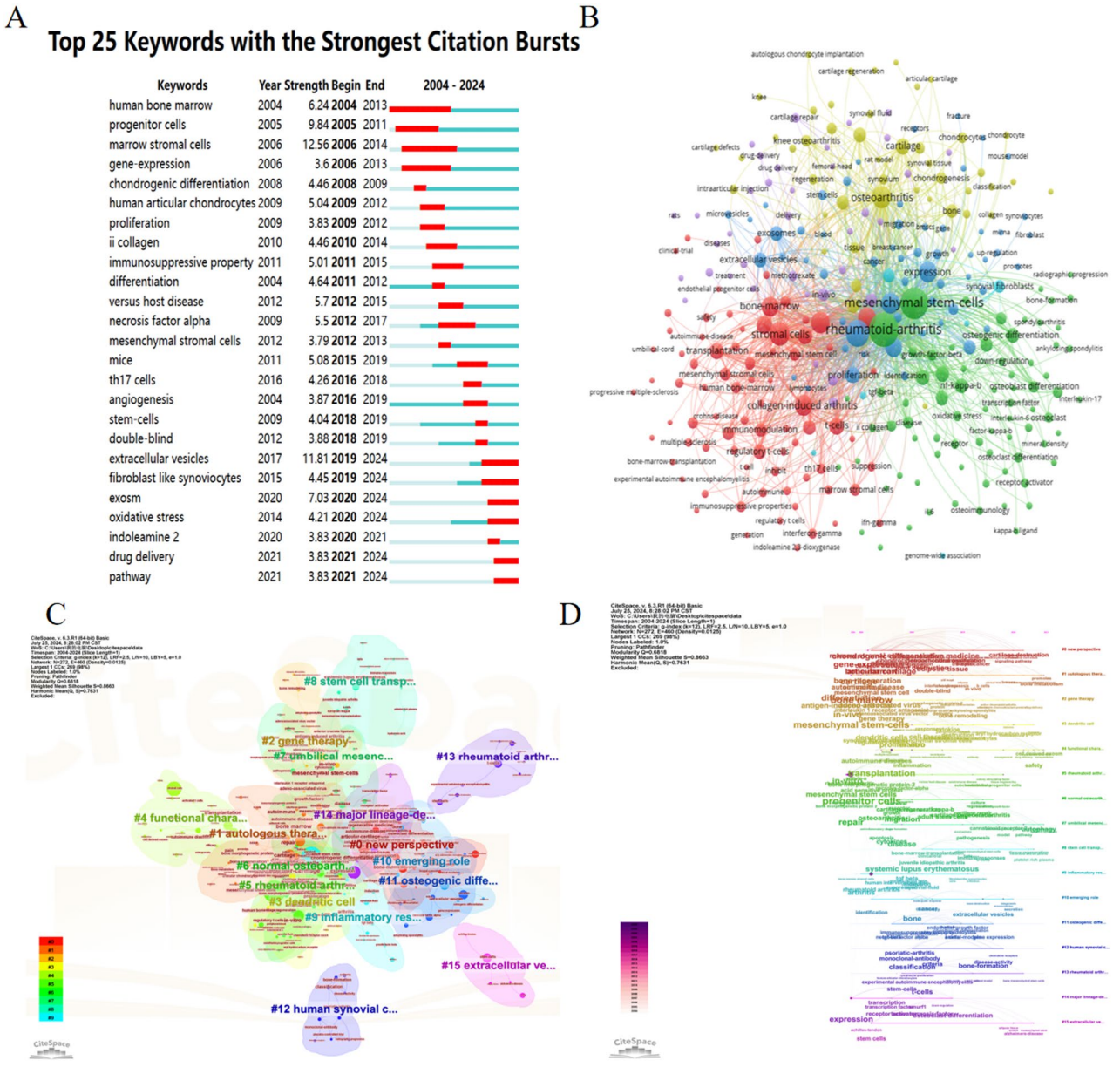

Fig. 5 Map of keywords. **A** MSCs therapy for RA keyword breakout map. **B** MSCs therapy for RA keyword clustering network. **C** MSCs therapy for RA keyword co-occurrence network. **D** MSCs therapy of RA keywords time graph

guidelines. The map is consistent with the results of the development process of stem cells. Since 2019, based on previous research, we have further explored the relevant mechanisms of MSCs in treating RA. Moreover, extracellular vesicles (EV) is an important hotspot in the current research on the treatment of RA by MSCs. Its hotspot intensity is as high as 11.81. It is expected to become a hot research direction for many researchers in future related studies [23, 24].

Keyword co-occurrence analysis

VOSviewer parameters were set as follows: Method (Linlog/modularity) and a minimum number of documents of keyword:8. The obtained results were retrieved for 242 (Fig. 5B). These keywords can be divided into five clustering blocks that overlap and run in parallel with each other.

There are 66 keywords in the red block. This set mainly includes adipose tissue, autoimmune, autoimmune-disease, B-cells, bone marrow transplantation, cell therapy, dendritic cell, endothelial cell, regenerative medicine, immune modulation, IFN-gamma, immune responses, marrow-stromal cell, lymphocyte-proliferation, and umbilical cord blood et al. The red block among which "stromal cells" is the keyword with the highest citation frequency in this set. Adipose tissue, bone marrow, and

umbilical cord blood are the three important sources in the current research of MSCs. Relevant research has been carried out on the connection between MSCs and dendritic cells (DC). It is also pointed out that MSCs can play a role in various diseases such as immune modulation, inflammatory bowel disease, lupus erythematosus, and multiple sclerosis, and clinical trials and related safety research have been carried out.

There are 58 keywords in the green block. This set mainly includes, rheumatoid arthritis, ankylosing spondylitis, antigen induced arthritis, bone destruction, bone metalism, bone generation, bone remodeling, bone-formation, bone-resorption, chemokines, colony-stimulating factor, down-regulation, genome-wide association, Ⅱ-collagen, inflammatory arthitis, kappa-bligand, bone mineral density, osteoblast, osteoblast differentation, osteoclast, osteoclastogenesis, osteoimmunology, osteoporosis, oxidative stress, psoriatic-artheitis, rankl, and synovial fibroblast et al. The green bolck among which "rheumatoid arthritis" is the keyword with the highest citation frequency in this set. Collagen-induced arthritis is a commonly used model for RA. Researches have been conducted on bone destruction, bone metabolism, bone regeneration, bone resorption and the expression levels of related genes in the RA model, exploring the relationships between MSCs and osteoblast differentiation, osteoclastogenesis and immune modulation, in order to clarify whether MSCs can be associated with the treatment of RA.

There are 44 keywords in the blue block. This set mainly includes rheumatoid arthritis, activation apoptosis, articular chondrocytes, autophagy, cytokines, hypoxia, identification, immunosuppression, induction, inflammation, inhibit, macroohage, mechanism, metastasis, migration, pathogenesis, pathway, proliferation, promote, receptor, responses, and suppression et al. The blue bolck among which "rheumatoid arthritis" is also the keyword with the highest citation frequency in this set. The difference from the green block is that this block explores the relevant mechanisms and signal pathways between the migration of MSCs and RA in terms of immunosuppression, introduction, and inflammation from the perspectives of articular chondrocytes, synovial fibroblasts, and macrophages.

There are 43 keywords in the yellow block. Related words such as methotrexate and drug-delivery appear, establishing the relevant connection between the efficacy of MSCs in treating RA and clinically commonly used drugs.

There are 30 keywords in the purple block. The words "joint", "tissue engineering" and "matrix" appear in this set, indicating that the related combined applications of MSCs in the treatment of RA and the application of MSCs-derived exosomes have emerged.

Keyword clustering analysis

Cluster analysis was performed on the keywords in the 1296 screened papers by using Citespace. Cluster analysis is to gather the keywords with closer distances together to form clusters with independent concepts. The similarity of attributes within clusters is the largest, and the similarity between clusters is the smallest [25]. The clustering modularity value (Q) is 0.6818 (>0.4), indicating that the clustering is effective. The average silhouette value (S) is 0.8663 (>0.5), indicating a high network homogeneity, close connections between keywords, and reasonable clustering. As shown in Fig. 5C; Table 2. The clustering shows a total of 16 clusters, covering 16 categories such as the new perspectives of MSCs in the treatment of RA, the potential of autologous treatment, the cellular and functional characteristics of mesenchymal stem cells, rheumatoid arthritis, umbilical cord mesenchymal stem cells, stem cell transplantation, inflammatory response, emerging roles, osteogenic differentiation, synovial cell populations, rheumatoid arthritis, master lineage determinants, and extracellular vesicles. Conduct a time axis span analysis for each cluster block under the CiteSpace algorithm to obtain the keyword cluster timeline graph, as shown in Fig. 5D. The time line chart intuitively shows the annual dynamic change trend of a group of research hotspots represented by a certain key, and shows the rise and fall of hotspots in this clustering research direction. The keywords of the same cluster are from left to right and from far to near on the same horizontal line. Among them, the time span of the first cluster, which is the new perspectives of MSCs in the treatment of RA, is the longest, reflecting that exploring the multi-angle treatment of MSCs in the treatment of RA has always been one of the mainstream research directions for researchers. The cluster of human cell synovial populations has the shortest time span. The literature suggests that the research on the relevant mechanism of MSCs in human cell synovial populations in clinical trials involves moral and ethical issues. Therefore, it has not attracted widespread attention from researchers at present. Through the analysis of the three most frequently cited keywords in each cluster, it is concluded that collagen-induced arthritis is a commonly used model for MSCs in the treatment of RA. NF-κB, whose self-regulation plays a crucial role in the immune response to infection, is an important factor in the research on MSCs for the treatment of RA. A large number of in vivo and in vitro experiments have been carried out on the functional characteristics of MSCs to prove the differentiation ability of MSCs. Subsequently, most of the subsequent studies basically analyzed the impact of MSCs on the treatment of RA from the perspective of the differentiation and activation abilities of MSCs. Currently, the main source of MSCs is bone marrow mesenchymal stem cells. In 2024, it still remains a

Table 2 Keyword clustering cluster information based on cite space

Cluster ID	Size	Silhouette	mean(Year)	Label
0#	31	0.713	2012	Mesenchymal stem cell, rheumatoid arthritis, human mesenchymal, chondrogenic, differentiation therapeutic, Potential collagen, induced, synovial fluid, clinical application, degenerative arthritis
1#	30	0.923	2012	Mesenchymal stem cell, rheumatoid arthritis, collagen-induced arthritissynovial, synovial fluid, extracellular vesicle, human adipose, tissue-derived, human bone marrow
2#	23	0.854	2010	Gene therapy, recombinant, adeno-associated virus, skeletal gene therapy, musculoskeletal repair, Joint, mesenchymal stem cell, abnormal, condition, instructive, cartilage, regeneration modalities
3#	23	0.768	2013	Mesenchymal stem cell, rheumatoid arthritis, bone marrow, cell-based therapy, rheumatic diseases, inflammatory, receptor, th17 cell expansion
4#	21	0.972	2015	Bone marrow, therapeutic efficacy, collagen-induced arthritis, cell-based therapy, stromal cell
5#	21	0.872	2008	Fibroblast, marrow-derived, cartilage, degeneration, cartilage tissue engineering, rheumatic diseases
6#	19	0.737	2011	Extracellular vesicle, marrow-derived, b- cell, viability-supporting propertie, lysophosphatidic acid, therapeutic prospect
7#	18	0.908	2016	Exosome, bone erosion, marrow-derived, t cell, Umbilical mesenchymal stem, efficient reduction
8#	14	0.921	2016	Vivo environment, musculoskeletal system, using cell therapy, injured tissue stem cell, Transplantation, autologous stem cell, transplantation, various adult, Pediatric, adipose
9#	13	0.857	2010	Human adipose-derived, inflammatory, jioint diseases, marrow-derived, regulatory t cell, joint
10#	12	0.956	2014	Emerging role, adipose-derived mesenchymal stem cell, collagen-induced arthritis, cell-derived exosome, cell-based therapy,
11#	12	0.898	2012	Osteogenic, differentiation, ankylosing spondylitis, morphogenetic protein, indoleamine
12#	9	0.932	2012	Ankylosing spondylitis, osteoblast differentiation, cytometric characterization, human synovial cell population, controlling memoryt cell response, marrow-adherent cell
13#	9	0.975	2013	Clinical trial, uppressive effect stromal cell, negative effect, secreting cytokine, positive effect, early-stage differentiation
14#	8	0.948	2009	Bone erosion, recent development, mesenchymal stem cell, inflammatory arthritis, transcription factor
15#	6	0.968	2015	Extracellular vesicle, cell-derived, inflammation-related condition, tissue repair, molecular target, therapeutic potential

high-frequency research hotspot, indicating that bone marrow mesenchymal stem cells will continue to be a research hotspot in the future. In the recent three years, adipose-derived mesenchymal stem cells and umbilical cord-derived mesenchymal stem cells have emerged as new perspectives for MSCs in the treatment of RA. Word cloud map was drawn according to the frequency of keywords in order to intuitively reflect the current research hotspots of MSCs and RA (Fig. 5E). Currently, the efficacy outcomes of MSCs in treating RA are observed based on their abilities of in vivo cell differentiation and bone reconstruction. MSCs have begun to be used as one of the treatment methods for osteoarthritis, with rheumatoid arthritis and knee osteoarthritis as the main research directions. From the perspective of autoimmune diseases, MSCs can also be transplanted to treat autoimmune diseases such as systemic lupus erythematosus and rheumatoid arthritis by inhibiting the expression of tumor necrosis factor and promoting the differentiation of osteoblasts.

Analysis of basic research and clinical research

Preclinical research section

In preclinical research, it has been found that MSCs can delay the pathological process of RA in four major aspects: inhibiting bone erosion, regulating innate and adaptive immunity, regulating oxidative stress, and inhibiting angiogenesis (Table 3).

Bone erosion reduction MSCs can inhibit bone erosion, maintain the integrity of joint structure and improve joint function by regulating FLS. Studies have shown that intracapsular injection of MSCs can reduce the levels of inflammatory factors (IL-1β and IL-6) in the joint cavity synovial fluid and inhibit the destruction of joint cartilage through suppressing the migration of FLS [26].Platelets can promote FLS to secrete MMPs, thereby leading to the erosion of cartilage and bone. MSCs can prevent the interaction between aggregated platelets and FLS by releasing plasminogen activator inhibitor-1 [27].MSCs can also alleviate the FLS-mediated osteoclast differentiation and improve the tibial bone erosion in CIA mice, by producing osteoprotegerin to bind to the surface receptors of osteoclasts or inhibit the expression of RANKL in FLS cells through the CD39-adenosine signaling pathway [28–30].

Immunoregulation MSCs can collaboratively regulate innate immunity (macrophages, neutrophils and dendritic

Table 3 Preclinical efficacts of MSCs in the treatment of RA

Route of administration	Dosage of administration	Type of stem cells	In vivo experiments or in vitro experiments	Outcomes	References
intra-articularly injected	10^6 cells/8μL	embryonic stem cell-derived MSCs	In vivo experiments and in vitro experiments	The CD4 + T cell↑,multinucleated cells ↓,cathepsin K↓,RANK↓ ,ATP6v0d2↓,inflammation↓ erosion↓,Il-1β↓,Il-6↓TNF-α↓,Treg/Th-17 ratio↑,the frequency of CD4 + CD44 + T cells reactive↓	[26]
injected intraperitoneally	1×10^6 human AT-MSCs/100μl	BM-MSCs	In vivo experiments	Hind limb thickness↓,pathological scores of synovitis↓,FOX3P + CD25 + Treg cell↑,TNF-α ↓,anti-CII antibody↓,IL10↑	[39]
intravenous injection	2×10^6 cells, 3×10^6 cells	hUCB-MSCs	In vivo experiments	TNF-α↓,IL-1↓,IL-6↓,IL-10↑,CD4 + CD25 + FOXP3 + Treg cells↑	[27]
intravenously through the lateral tail vein	1×10^6 cells/rat/dose	BM-MSCs	In vivo experiments	RF↓,CRP↓,IL-1β↓,TNF-α↓,IL-17 ↓,ADAMTS-5↓,IL-4↑,TIMP-3↑,TGF-β↓,GSH↑,GST↑,LPO↓	[38]
intravenous injection	2×10^6 GMSCs for each mouse	GMSCs	In vivo experiments	BMD↑,Ct.Ar↑,BV/TV↑,SA/V↓,Bone Mechanical Integrity↑,Load-bearing Function↑,Tibia Stiffness↑,Localized Deformation/Strain↓ Surface Roughness-related SA/V↓	[28]
intravenous injection	2×10^6	hUCB-MSC	In vivo experiments and in vitro experiments	Full-length TNFR1 in siTNFR1-MSCs↑,MCP-1 secretion↑,CXCL9, CXCL10, RANTES, IL-8↓ Growth factors↓,Cellular TNFR1 level↓,Cellular TNFR1 level↓,sTNFR1 secretion↓,Pathological severity↓,Inflammatory cytokines in serum↓,Paw thickness↓,sTNFR1 in peripheral blood↓	[31]
tail intravenus injection	1×10^7 hESC-MSCs	HES-MSCs	In vivo experiments and in vitro experiments	The swelling in the joints (ankle, knee)↓,Inflammation↓MImmune cell infiltration↓,CD4 + T cells↑,Foxp3 + Treg cells↑,pro-inflamma-tory T helper 17 cells↓,interleukin-10↑interleukin-4↑ The proliferation rate of T cells↓,the interferon-γ -secreting potential↓,lung fibrosis↓,protein expression of a-smooth muscle, actin, which is related to fibrosis↓	[92]
injected intravenously	1×10^6 cells/100μL/mouse	HNTSCs	In vivo experiments and in vitro experiments	Arthritis severity scores↓ ,incidence of arthritis↓,CD4 + CD25 − T cells↓,Osteoclastogenes↓ KRTAP1-5,HAS2,CXCL1↑;GSTT2B and C4B↓	[36]
intravenous injection	2×10^6 ADSCs	ADMSCs	In vivo experiments and in vitro experiments	NF-κB p65/,p50↓,P65/50↓,RANKL↓osteoclastsgenesis↓	[93]
		BMSCs	In vitro experiments	BMP2↓,Il-8↑,neutrophils↑	[34]
intra-articular injection	6×10^5 ADSCs (passages 4 to 6)	ADMSCs	In vivo experiments and in vitro experiments	RA progression↓,promotes, the reconstruction of the CX3CR1+	[33]
		ADMSCs	In vitro experiments	CD69↑,IL-17AF↑,IL-17 A↑,IL-17 F↑,$CD4^+$T↓,IL-1Ra↑	[37]
tail vein infusion	2×10^6个 hUC-MSC	hUC-MSC,	In vivo experiments	IL-6↓,TNF-α↓	[94]
intravenous infusion intra-articular injection	GMSCs (2×10^6cells)	GMSCs	In vivo experiments and in vitro experiments	Ly6G + neutrophils↓,NETs↓,PGE2↑,p-PKA↑,p-ERK↓,IL-6 、TNF-α↓	[95]
MSCs encapsulated in 1.0%, 2.5%, and 5.0% 3Dalginate hydroge		MSCs	In vitro experiments	$CD86^+$↓,MHC Ⅱ$^+$↓,$CD39^+$↑,$CD73^+$↑,IL-6↓,TNF-α↓,IL-10↑	[35]

Table 3 (continued)

Route of administration	Dosage of administration	Type of stem cells	In vivo experiments or in vitro experiments	Outcomes	References
intravenously via tail vein	5% chloral hydrate, 0.1 mL of complete Fresno adjuvant and 400 μg of bovine type II collagen	BMSCs/ GFP-BMSCs	In vivo experiments and in vitro experiments		[30]
intravenously via tail vein	200 μl(1×10^6)HUMSCs	HUMSCs	In vivo experiments	CD105(+),CD90$^{+/-}$,CD73$^{+/-}$,HLA-DR$^{+/-}$,CD11b$^{+/-}$,CD19$^{+/-}$,CD34$^{+/-}$,CD45$^{+/-}$,AI↓,IL-10↑,TGFβ1↑,IL-17A↓,IL-1β↓	[96]
		DPSCs	In vitro experiments	STRO-1(+),c-Kit$^{+/-}$,PD-L1↑,IFN-γ↓,TNF-α↓,IL-2↓,CCL5↓,CXCL10↓,IL-6↑	[97]

cells) and adaptive immunity ($CD4^+$ T cells), and reestablish the balance of the local immune microenvironment in the affected joint of RA mice. MSCs can affect macrophages through two major aspects: secreting soluble factors and regulating mitochondria. MSCs promote the polarization of M2-type macrophages through paracrine cytokines, such as IL-10, ProstaglandinE2 (PGE2) and transforming growth factor-β (TGF-β) [31], and induce the apoptosis of M1-type macrophages via the caspase-8/9/3 signaling pathway [32]. In addition, during the progression of RA, the proportion of CX_3CR1^+ macrophages with high expression of Atf3 and Ccl3 (impaired oxidative phosphorylation and pro-inflammatory) increases. MSCs can reduce this pathological subpopulation through mitochondrial transfer (via tunnel nanotube, TNT) and repair the function of $CX3CR1^+$ macrophages [33]. Moreover, PGE2 secreted by MSCs can also inhibit the formation of neutrophil extracellular traps through the PGE2-PKA-ERK axis to reduce joint inflammation [34]. MSCs may differentiateTolerogenic dendritic cells (tolDCs) and Treg cells through A2A/2Br-mediated differentiation and alleviate inflammatory tissue damage [35].

The regulation of the adaptive immune system is mainly reflected in the regulation of the imbalance of $CD4^+$T cell subsets. IFN-γ in the RA inflammatory microenvironment binds to IFN-γ receptors on the surface of MSCs, significantly enhance the ability of MSCs to secrete indoleamine 2, 3-dioxygenase (IDO), which catalyses the decomposition of tryptophan and promotes the proliferation of CD4 + CD25- effector T cells [36, 37]. Experiments have demonstrated that MSCs can significantly inhibit the proliferation of $CD4^+CD44^+$T cells, thereby suppressing the type II collagen-mediated immune response of the body and reducing autoantigen-mediated immune attack, fundamentally delay the immune-driven progression of RA [26].

Oxidative stress alleviation MSCs can enhance antioxidant capacity by promoting the expression of glutathione and increasing the activity of glutathione-S-transferase, alleviate the damage to joint tissues caused by oxidative stress responses, further protect chondrocytes from reactive oxygen species (ROS) attacks in the inflammatory microenvironment, and maintain the stability and integrity of cartilage matrix [38].

Inhibit vascular proliferation MSCs can activate the PI3K/Akt pathway in FLS by secreting IL-10, down-regulate the transcriptional activity of the VEGF promoter, reduce VEGF secretion, cut off the nutritional supply of pannus, and inhibit the formation of pannus. Meanwhile, the transforming growth factor β (TGF-β) secreted by MSCs can bind to the TGF-β receptor on the surface of endothelial cells, inhibiting the migration ability of endothelial cells. The activation and migration of endothelial cells are inhibited, preventing the formation of a neovascular network that supports the growth of pannus [39].

Clinical research section

In clinical research, the treatment of MSCs mainly focuses on regulating the immune microenvironment (Table 4). In a Phase I trial of RCT undertaken by the Department of Rheumatology and Immunology ofDaping Hospital of Third Military Medical University, it was found that after intravenous infusion of human umbilical cord blood-derived MSCs to RA patients, the levels of IL-1β, IL-6, IL-8 and TNF-α in the serum of RA patients decreased within 24 h [40].After RA patients received MSCs treatment, the expression of the TGFB1 showed a time-dependent upregulation.TGFB1 can reduce the release of pro-inflammatory cytokines (such as IL-17 and TNF-α) by down-regulating differentiation-related transcription factors of Th1 and Th17 cells (T-bET and RORγt), thereby alleviating the attack of autoreactive t cells on joint tissues [41].Studies have shown that autologous MSCs also have a powerful therapeutic effect on innate immunity. Autologous MSCs transplantation can improve the clinical symptoms of patients with refractory RA by reducing the plasma concentration of BAFF/APRIL and the expression of BR3 and BCMA receptors

Table 4 Clinical efficacts of MSCs in the treatment of RA

Route of administration	Cell type	Dosage of administration	Outcomes	References
①MSCs: intravenous injection; ②IFN-γ: intravenous infusion/ intramuscular infusion	hUC-MSCs	①MSCs:1 × 10^6 wild-type mBM-MSCs,1 × 10^6 Ifngr1tm1Agt/J mBM- MSCs ②IFN-γ: Subjects received 1 × 10^6 cells/kg of body weight in 50 mL of 1% albumin in physiological saline via intravenous infusion with/without a single intramuscular infusion of 1 million IU of IFN-γ.	DAS28- ESR↓,HAQ-DI↓,ESR↓,CRP values↓,RFlevel↓,Treg/Th17 cell ratio↑	[90]
intravenous injection	BM-MSCs		TGFβ1↑,IL4↑,IFNG↑	[41]
intravenous administration	BM-MSCs	once 1 × 10^6 MSCs per kilogram of body weight	BAFF↓,APRIL↓,CD19 + B cells↓,BR3 + CD19 + B↓,BCMA + CD19 + B↓,	[42]
intravenous injection	BM-MSCs		CCL2 ↑,CCL5 ↓	[43]
intravenous infusion	BM-MSCs	1 × 10^6 allogeneic BM-cMSCs per kg of body weight (maximum 70 × 10^6 cells) executed three times with 4-week intervals.	VAS↓,ACR↓,SDAI / CDAI↓(3),RF(3¯ /3—),anti-CCP↑,ESR↓,CRP↓,IL-10↑,IL-17↑,TNF-α↑,Treg/Th17 ratio (3↑3↓),CD90/CD105/CD73(¯),CD34/CD45/CD14/CD79a(—)	[98]
intravenous infusion	AD-MSCs	2 × 10^8 adMSCs	ACR66/68↓,CRP↓	[99]

on the surface of B cells, thereby inhibiting the proliferation and activation of B cells, and reducing the autoantibodies production [42].Moreover, one month after autologous MSC transplantation treatment, the expression of the plasma CCL5 significantly decreased, suggesting that CCL5 may be one of the key targets for MSCs to alleviate RA inflammation [43].Clinical studies have also found that the injection methods of MSCs (intravenous injection or intra-articular injection) have no statistically significant difference in clinical efficacy. However, intravenous injection can reduce the therapeutic effect of MSCs, and cause the cells to accumulate in the lungs, liver and spleen [44].

Discussion

General information on MSCs in RA treatment

As shown in Fig. 1B, the studies on MSCs in the treatment of RA spans across ten disciplines, *with* the top three being cell biology, biochemical molecular biology, and immunology. According to the analysis of published research on MSCs in RA treatment (Fig. 2A), global literature output in the single digits during 2004–2005, indicating that this research was in its early exploratory stage. Although the literature output decreased in 2011, it exhibited an overall increasing trend, reflecting a growing recognition of the research value of MSCs in RA treatment. At present, China and the United States of America are leading the field (Fig. 2D). The regulatory policies regarding stem cells, which vary across countries, are also key factors affecting the national research output. the United States of America implements a tiered management system, while stem cell research across the 27 EU member states is governed by EU regulations. China operates a dual-track system, which is similar to that of Japan. Variations in management systems also result in differences in stem cell standardization and clinical application guidelines, creating challenges for cooperation and communication between countries, regions, and institutions, and reducing academic exchanges [45]. This is mainly reflected in the decline of publications in 2011. However, with the gradual liberalization of national policies and the continuous introduction of regulatory guidelines related to stem cell therapy, international collaboration has increased [25]. Substantial financial investments, combined with the accumulation of foundational scientific research and clinical trial data from various research institutions, have laid a good theoretical foundation for the development of MSCs in RA treatment. As a result, the number of published papers has steadily increased. Among the top 10 research institutions, the Chinese Academy of Sciences, Sun Yat-sen University, Harvard University, and the University of California stand out as influential institutions with higher levels of research output. Professor Christian Jorgensen and Professor Daniele, leaders of output. Montpellier Institute of Regenerative Medicine and Biotherapy, are key contributors to the study of MSCs in RA treatment. Their research team has demonstrated the therapeutic potential of MSCs for various rheumatoid and autoimmune diseases, including RA. The team focuses on developing optimized treatment strategies for rheumatic diseases by selecting MSC subtypes with higher regenerative potential through advanced omics approaches and generating engineered MSCs with enhanced properties. Professor Christian Jorgensen has authored more than 70 publications on rheumatism in the field of immunology and stem cell therapy. His work has appeared in several high-impact journals, including *Blood*, *Annals of*

the Rheumatic Diseases, and *Nature Reviews Rheumatology*. He proposed that the extracellular vesicles from aging mesenchymal cells were defective and could not prevent osteoarthritis [46]. Meanwhile, immunosuppression remains an inevitable potential side effect in clinical research. However, this has not prevented the application of MSCs in various research fields [47]. MSCs from various sources possess the ability to differentiate into three cell lines and most importantly, can effectively regulate immune response and promote healing. Additionally, he pointed out that the mechanism of MSCs differentiation, immunomodulation, and paracrine characteristics are currently one of the directions of extensive research. It is precisely due to the unique role of MSCs that their application in RA is possible [48]. In the author cooperation network diagram (Fig. 3C), no authors have a media centrality score of 0.1 or higher, indicating a lack of in-depth researchers in this field, and an absence of strong collaborative relationships among authors. The *International Journal of Molecular Science* (42 articles, 3.2%) and *Frontiers in Immunology* (38 articles, 2.9%) were the most frequently published journals on MSCs in RA treatment (Fig. 4A). Although more than 200 journals have published research in this field, there is no significant proportion of journals. Therefore, there is currently no dedicated high-quality, high-impact journal for scholars to submit relevant literature on MSC-based on RA treatment. In the list of supporting funding sources (Fig. 4B), the National Natural Science Foundation of China and the Natural Health Foundation of the United States of America have funded the highest number of publications, reflecting the strong support from China and the United States of America in this research area. In the co-cited journals (Fig. 4C), studies from journals in molecular science, biology, immunology, and clinical medicine are frequently cited, with molecular science and biology accounting for a larger share. This indicates that MSC-based RA treatment remains primarily focused on basic research, and related clinical experiments have appeared. At present, many countries, including the United States of America, Japan, and members of the EU, have approved stem cell-based products for clinical use. By developing stem cell therapies derived from different sources, these countries have introduced products for the treatment of acute myocardial infarction, degenerative osteoarthritis, Crohn's disease, and other diseases. These advancements provide a useful approach for the clinical use of MSCs in the treatment of RA-related stem cell products. Overall, compared with other fields, the number of publications on MSCs in RA treatment remains relatively low, highlighting significant research potential and value. With the continued strong support from national policies and research funding, MSC-related research and technological advancements are expected to progress rapidly, leading to deeper insights and broader applications in the future.

Research hotspots and frontiers of MSC therapy for RA

Hot research trends of MSCs in RA treatment

Based on the time distribution of keywords related to MSCs in RA treatment, research has progressed through three stages: from studying the related functional characteristics of MSCs to investigating their therapeutic effects of MSCs in RA treatment, followed by in-depth exploration of treatment mechanisms, signaling pathway, and the functional characteristics of MSCs-EV. This progression reflects an orderly and continuous development. For MSCs themselves, research has progressed from examining their own functional characteristics to exploring the functional properties of EVs. For the mechanism of RA treatment, studies have shifted from investigating the effects of MSCs on RA to examining the role of EVs in RA therapy, reflecting the deepening and expansion of the research scope of MSCs in RA treatment.

Functional characteristics of MSC$_S$

In the study of MSCs themselves, it has been proposed that MSCs have the ability to differentiate into progenitor cells and self-renew, with progenitor cells further differentiating into related specialized cells to maintain the balance of cellular microenvironment in vivo. Currently, bone marrow stromal cells extracted from human bone marrow are the main research focus. MSCs regulate innate immunity and adaptive immunity by reducing the populations of DC, macrophages, natural killer cell, B cells, and T cells, while promoting an anti-inflammatory phenotype [49]. MSCs mediate the hypoxic activation of apoptotic factors through Caspase 3, enabling immune cell recruitment at stem cell injection sites and further phagocytosis by macrophages with local circulation functions [50]. MSCs can also regulate immune characteristics through cell-to-cell contact and the secretion of soluble factors [51]. The effects of continuous passage of MSCs in vitro on gene expression and immunosuppression have been explored in related in vitro experiments. It has been confirmed that during the co-culture of MSCs with T cells, B cells, and Treg cells, the number of Treg cells expressing CD4+, CD45+, and FOXP3 phenotypes increased threefold, while TNF-α secretion mediated by CD3 + T cells was inhibited [52]. IFN-β further enhances the immunomodulatory characteristics of MSCs by increasing the expression of immunomodulatory molecules secreted by MSCs [53]. In animal studies, particularly in collagen-induced arthritis (CIA) mice, osteoblasts and osteoclasts are balanced under healthy conditions, while osteoclast activity is up-regulated in RA [54]. MSCs have the ability to differentiate into osteoblasts and osteoclasts, inhibiting rankl-induced osteoclast

fragmentation, reducing osteoclast precursors in bone marrow, and effectively inhibiting systemic bone loss in mice [55]. At present, the immune suppression characteristics of MSCs are mainly studied in relation to Th17 cells. According to the CXCR-4 expressed on the MSC for targeting inflammation, and providing a new solution for MSCs-based RA treatment, potentially meeting clinical anti-inflammatory needs [56].

Inflammatory mechanism of MSCs in RA treatment

CIA is a common model for studying MSCs-based RA treatment. In the CIA mouse model, MSCs encapsulated by alginate gel can induce immature DC to transform into tolDCs by activating the adenosine A2A/2B receptors, further regulating T cells into Tregs. This process induces significantly higher expression of CD39 + and CD73 + on MSCs, thus improving arthritis inflammation [35]. MSCs derived from bone marrow can migrate to synovium of joints, though the molecular mechanism of this migration remains unclear. A comparative study of MSCs from multiple tissue sources, including bone marrow MSCs, in the treatment of RA found that synovial MSCs were more likely to form in cartilage [57]. NF-κB and TNF-α play an important role in the self-regulation of immune response and are key factors in studying of MSCs in RA treatment. Short-term exposure to TNF-α can induce human osteoblasts to differentiate adipose-derived MSCs into osteoblasts. Additionally, TNF-α signaling reduces the repair response of endogenous joint MSCs, thereby limiting cartilage and bone regeneration during RA [58]. As a key cell type in the joints of patients with RA, fibroblast-like synoviocytes (FLSs) have been suggested to originate from the same progenitor cells as MSCs. The interaction between FLSs, MSCs, and immune cells may contribute to the chronic and progressive nature of RA [59, 60]. Therefore, whether MSCs exert a therapeutic or destructive exert in RA treatment depends on specific conditions and requires urther investigation.

Development prospect of MSC_5 extracellular vesicles in RA treatment

Chen et al. were the first research team to report bone marrow MSC-EVs, and their study confirmed that injecting miR-150-5p of bone marrow MSC-EVs into joint cavity could effectively reverse the migration and invasion of RA-FLS [61]. Since then, increasing numbers of research teams have found that EVs can regulate the maturation of DC and regulate their functions [62]. The ability of miRNA contained in EVs to be transported is considered a key mechanism by which MSCs exert their regulatory effects. EVs can also promote the polarization of monocytes and macrophages toward an anti-inflammatory phenotype, helping maintain the balance between pro-inflammatory and anti-inflammatory cytokines [63]. In CIA mouse model, intraperitoneal administration of MSC-EVs reduced immune response, joint inflammation, synovial hyperplasia, and the degeneration of articular cartilage and adjacent tissues [64]. By changing the culture methods of MSCs, such as through hypoxia [65, 66], mechanical stimulation [67], 3D culture [68], induction with drugs and chemical reagents [69, 70] and cytokine induction [71–74], the beneficial effects of MSCs can be further enhanced. Studies have shown that MSC-EVs from IFN-β culture effectively reduces the expression and release of RA-related cytokines, preserves T cell population, reduce T cell versatility, and inhibit RA-FLS migration [75]. As more attention is paid to MSC-EVs in inflammatory diseases, their future development is expected to attract even more interest from researchers than MSCs themselves.

The weaknesses of MSCs in RA treatment and suggestions

MSCs have become a prominent research focus over the past 20 years. Although the number of related publications has grown significantly, the annual publication volume has not exceeded 200 papers. An analysis of the relevant literature reveals several challenges in the current research of MSCs: As a type of adult stem cells, MSCs are more difficult to isolate and purify compared with embryonic stem cells. There is a need to identify effective methods for isolating and purifying MSCs to ensure higher purity [76, 77]. Controlling the differentiation of MSCs remains another significant issue. MSCs tend to differentiate after proliferating in vitro for a period of time [78, 79]. Maintaining their proliferation without differentiation over extended passages is an important challenge. While studies have explored the differentiation of mouse embryonic stem cells into various cell types, including neural cells, blood cells, cardiomyocytes, smooth muscle cells, striated muscle cells, bone cells, chondrocytes, mast cells, adipocytes, and even islet cells, the molecular mechanisms that control the differentiation of stem cells into these different lineages remain poorly understood. In animal experiments, no obvious rejection reactions have been observed with animal-derived MSCs. However, it remains unclear whether a rejection reaction would occur after transplantation into the human body, which represents a major bottleneck. Additionally, obtaining approval for studies using human-derived MSCs in RA animal models is often difficult due to ethical concerns, further hindering research progress [80]. The potential impact of rejection reactions on therapeutic outcomes is yet to be fully explored. If MSCs are injected into the non-lesion sites of the RA animal model, such as abdominal cavity and tail vein injection, whether they can accurately migrate to lesion site still needs further investigation [81, 82]. Meanwhile, the effectiveness of MSCs is often limited

by the bone immune microenvironment characterized by elevated reactive oxygen species/nitrogen (ROS/RNS) and hypoxia. To prolong the benefits mediated by MSCs, it is necessary to standardize the injection dose and frequency of MSCs to avoid skeletal muscle lesions caused by frequent injections [83].Encapsulation of mesenchymal stem cells transfected with IL-1 receptor antagonist genes has been proven to provide a sustained therapeutic effect for up to 30 days [84].To enhance the therapeutic effect of MSCs in the treatment of RA, researchers have adopted strategies such as drug loading [85], traditional Chinese medicine intervention [86, 87], and hydrogel encapsulated [88, 89].to increase the anti-inflammatory level of MSCs and prolong the therapeutic effect. The different legal standards and application guidelines for stem cell research across different countries and regions, as well as concerns about the reliability of stem cell source quality sources and the protection of donor privacy, present obstacles that prevent extensive cooperation among relevant research institutions. Currently, relevant institutions in China are members of the International Society for Stem Cell Research and the International Stem Cell Resource Bank Alliance. They are accelerating the standardization construction of stem cell-related resource banks and promoting the development and integration of unified standards both domestically and internationally. Despite the ongoing challenges and hurdles, some successes have been achieved, laying a cooperative foundation for the future treatment of RA with MSCs.

The clinical trials of intra-articular injection of MSCs included in this bibliometrics show that intra-articular implantation in the knee joint is safe and well tolerated, but the long-term efficacy is insufficient [90]. Clinical research on the treatment of RA with MSCs is gradually being carried out. Clinical research on the treatment of RA with MSCs lacks large-sample, multi-center, randomized trials. Moreover, the relevant evidence for the injection method is clearly insufficient, and high-level evidence-based evidence is still needed to provide a basis for clinical transformation. More RA patients from different regions and at different disease stages need to be included to verify the universality of the treatment efficacy. To conduct in-depth research on the survival time, distribution pattern and variability of MSCs in vivo and their impact on therapeutic efficacy, and to analyze the correlation between baseline characteristics of patients (such as IFN-γ levels and immunotyping) [88, 91] and the response to combination therapy, so as to provide a basis for individualized treatment (such as screening the most suitable patient group for combination therapy).

Over the past 20 years, an analysis of countries, research institutions, researchers, literature journals, and project fund support shouws that the cooperative relationships at different levels, including those among countries, institutions, and researchers, have developed from an initial point-like distribution to a network-like distribution. Support for MSCs in the treatment of RA has also been steadily increasing. However, in general, international cooperation remains insufficient, with relatively low cooperations. In the context of building a community with a shared future for mankind and advocating win-win cooperation, all countries should strengthen international exchanges and cooperation. On the basis of equality, mutual benefit, sharing, and cooperation, relevant researchers should be actively encouraged to form professional, open, and sharing social organizations. This is essential for promoting the standardized, specialized, and large-scale development of MSC research in treating RA. During these exchanges and cooperations, countries should share resources, build a comprehensive and multi-level academic environment, promote coordinated innovation development, and foster a favorable academic atmosphere for MSC-based RA research.

Addressing the above-mentioned weaknesses and existing research gaps requires in-depth research and mutual exchange among researchers. Establishing a unified global stem cell implementation standard is an issue that needs urgent attention. Only by establishing a unified standard can countries foster more extensive and deeper cooperative relationships, thereby advancing the use of MSCs in RA treatment to new heights.

Conclusion

The research of MSCs in RA treatment has experienced a benefit trigger period and a rapid growth period. With the continuous improvement of the system and the support of various funds, it has now entered a stable development period. EVs is the main focus of current research. The combination of MSCs with drug therapy and EVs will become the mainstream direction of future research and is emerging as a key word. In the future, efforts should be made to establish a unified and standardized stem cell system to promote extensive and in-depth cooperation and exchanges among countries. Fully explore the potential value of mesenchymal stem cells in the treatment of rheumatoid arthritis.

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Author contributions

WJ and TB put forward the research content. HJ, ZW, YZ and YL collected data. WJ, TB and HH rechecked the data. WJ, YZ and YL analyzed the data. WJ wrote the manuscript. YZ, TB, YL and HH reviewed and revised the manuscript. All authors contributed to the article and approved the submitted version.

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Data availability

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding authors.

Declarations

Competing interests

The authors declare no competing interests.

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