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ORIGINAL RESEARCH

A Bibliometric Analysis of Exosomes Associated with Rheumatic Diseases in the 21st Century

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Purpose: Numerous studies have suggested that exosomes are associated with rheumatic diseases, but no bibliometric analysis has been performed. This study presents the first comprehensive bibliometric analysis aiming to evaluate the current research hotspots and to anticipate future trends.

Methods: An electronic search was conducted in the Web of Science Core Collection (WOSCC) using exosome and rheumatic disease-specific terminology to identify eligible studies published from January 1, 2000 to October 19, 2024. Only English-language articles and review articles were selected for bibliometric analysis. Data analysis and visualization were conducted using CiteSpace 6.2.R3, VOSviewer 1.6.18, and the Bibliometrix R package.

Results: A total of 1,251 publications with 49,374 citations were extracted from the WOSCC database. Both publication and citation frequency increased steadily. 255 different countries or regions, 4,413 institutions and 7,213 authors contributed to the field. China and the USA are the leading countries and Shanghai Jiao Tong University has a significant influence. Théry C is the most frequently co-cited researcher. Most papers are published in Frontiers in Immunology, while Stem Cell Research & Therapy has the highest citations. Research is primarily concentrated in cell biology, immunology, and experimental medicine. Exosm, mesenchymal stem cells (MSCs), autoimmunity, regeneration, and others are major areas of research in this field. Research hotspots primarily focus on the diagnostic potential and therapeutic applications of exosomes in osteoarthritis and rheumatoid arthritis. Exosomes derived from MSCs and their cargo, such as microRNAs (miRNAs), have the potential to serve as biomarkers and therapeutic vehicles in these diseases.

Conclusion: This study firstly quantifies and identifies the current status and research frontiers of exosomes in RDs by using bibliometric analysis, which may provide valuable insights for researchers to navigate trends and emerging applications into the field.

Keywords: bibliometric, exosomes, osteoarthritis, rheumatoid arthritis, mesenchymal stem cells

Introduction

Exosomes are endocytic membrane-derived vehicles that ranging from 30 to 120 nm in size, identified as key mediators in intercellular communication.[1] Released by a variety of cell types, these vehicles are consistently found in bodily fluids such as breast milk, urine, plasma, and saliva.[2] Exosomes carry a diverse cargo, including proteins, lipids, DNA, and various RNA species.[3] Originating in endosomes, their biogenesis involves interactions with other intracellular vesicles and organelles, shaping their final content.[4] Each exosome reflects the characteristics and functions of its parent cell. The unique biological properties of exosomes enable them to protect internal biomolecules from deterioration and evade immune clearance, allowing for the delivery of more effective cargo with potential therapeutic targeting effects.[5]

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Moreover, exosomes can penetrate various biological barriers, including the blood-brain barrier, while their associated toxic side effects are minimized.[6,7]

Rheumatic diseases (RDs) encompass a range of disorders primarily targeting the musculoskeletal system, directly affect bones, joints, muscles, connective tissues, and periarticular soft tissue.[8] The primary pathobiological characteristic of many RDs is the development of an excessively self-reactive, antigen-driven immune response, which contributes to the complex inflammatory processes and tissue damage.[9] Due to the chronic nature of these disorders and the frequent adverse effects of conventional treatments, patients often seek complementary and alternative therapies, hoping for "less toxic" remedies.[10] Exosomes have been extensively studied for their role in RDs, particularly in relation to autoimmune and inflammatory conditions such as rheumatoid arthritis (RA), osteoarthritis (OA), and systemic lupus erythematosus (SLE). Exosomes derived from mesenchymal stem cells (MSCs), synovial fluid (SF), or immune cells carry proteins, lipids, and nucleic acids capable of modulating immune responses and tissue repair. Long non-coding RNAs (lncRNAs) in exosomes have been implicated in the pathogenesis of RA through the nuclear factor kappa B (NF-κB) and Wnt signaling pathways, with the resulting imbalance in Th17/Treg cell production contributing to synovial cell damage.[11] Exosome-derived miRNAs, such as miR-451a and miR-25-3p, are promising candidates for early diagnosis of RA.[12] Additionally, exosomal miR-26b-5p regulates the polarisation of macrophages and the hypertrophy of chondrocytes in OA.[13] Exosomes also help determine the cellular origin of disease onset. In the synovial fluid of patients with inflammatory arthritis, the most common exosomes are derived from platelets, T cells and B cells.[14] Exosomes from various sources demonstrate potential diagnostic and therapeutic effects in RDs. MSCs-derived exosomes have been shown to modulate immune responses and exhibit immune suppressive effects. Exosomal miR-16 and miR-21 secreted by bone marrow mesenchymal stem cells (BMSCs), as well as miR-146a-5p from umbilical cord mesenchymal stem cell (UC-MSCs) exosomes, promote the transition of macrophages to an anti-inflammatory M2 macrophage phenotype, thereby inhibiting the inflammatory response.[15] Exosomes are recognized as emerging leaders in regenerative medicine.[16] The integration of exosomes with biomaterials, such as hydrogels, has emerged as a novel therapeutic strategy. This approach not only lubricates joints but also serves as a drug delivery system, enabling sustained release of therapeutic agents.[17,18] Additionally, engineered exosomes modified with specific bioactive molecules can regulate corresponding target proteins, thereby enhancing anti-inflammatory and immunomodulatory effects.[19] For example, engineered exosomes over-expressing miR-140 target calpain 1, modulate mitophagy, and ameliorate OA progression via intra-articular delivery.[20] In conclusion, exosomes can influence RDs through various pathways.

Bibliometrics is a field of quantitative analysis applied to scholarly literature, capable of mapping intellectual structures, identifying research trends, and assessing scholarly impact. Its core value lies in providing a systematic method to measure and evaluate the vast output of scientific research, offering insights on the evolution of research and the interconnections between various research domains. However, recent studies suggested that exosomes hold significant potential in the treatment of RDs, and bibliometric analysis on exosomes in RDs have not yet emerged. This study aims to address this gap by performing a bibliometric analysis of exosomes associated with RDs in the 21st century. Our objective is to evaluate the current state of research to gain a better understanding of the research dynamics in this field. Additionally, we seek to predict future thematic development and research priorities by examining research trends and hotspots. This analysis will also emphasize the impact of exosomes on the diagnosis and treatment of OA and RA, underscoring the importance of continued research in this field.

Methods

Search Strategy and Data Collection

The literature source for this analysis is the Web of Science Core Collection (WOSCC), which is recognized for its comprehensive and standardized coverage of international scientific literature. The search strategy utilized the following search string: (TS=("rheumatic disease" OR "rheumatology" OR "rheumatism" OR "rheumatoid arthritis" OR "psoriatic arthritis" OR "osteoarthritis" OR "gout" OR "pseudogout" OR "arthritis" OR "Takayasu arteritis" OR "ankylosing spondylitis" OR "spondyloarthropathy" OR vasculitis OR "granulomatosis with polyangiitis" OR "Wegener granulomatosis" OR "microscopic polyangiitis" OR "Behçet" OR "systemic lupus erythematosus" OR "Sjogren's syndrome" OR "systemic sclerosis" OR "scleroderma" OR "connective tissue disease" OR "autoimmune disease" OR "myositis" OR "polymyositis" OR "dermatomyositis" OR "idiopathic inflammatory myositis" OR "antiphospholipid syndrome" OR "fibromyalgia" OR "Still's disease" OR "polymyalgia rheumatica")) AND TS=("exosomes" OR "exosome" OR "exosomal"). The time frame was restricted to the 21st century (January 1, 2000 to October 19, 2024). Only articles and review articles published in English were considered to maintain the academic rigor and linguistic consistency of the analysis. Duplicates were removed using CiteSpace. All highly cited papers indexed by the WOSCC were extracted into a table format. The data were downloaded and verified independently by two researchers (YYZ and SWW) to assure the accuracy of the study. Any discrepancies were addressed through the third-party (XYA). The flow chart depicted in Figure 1 illustrates the data extraction and analysis process.

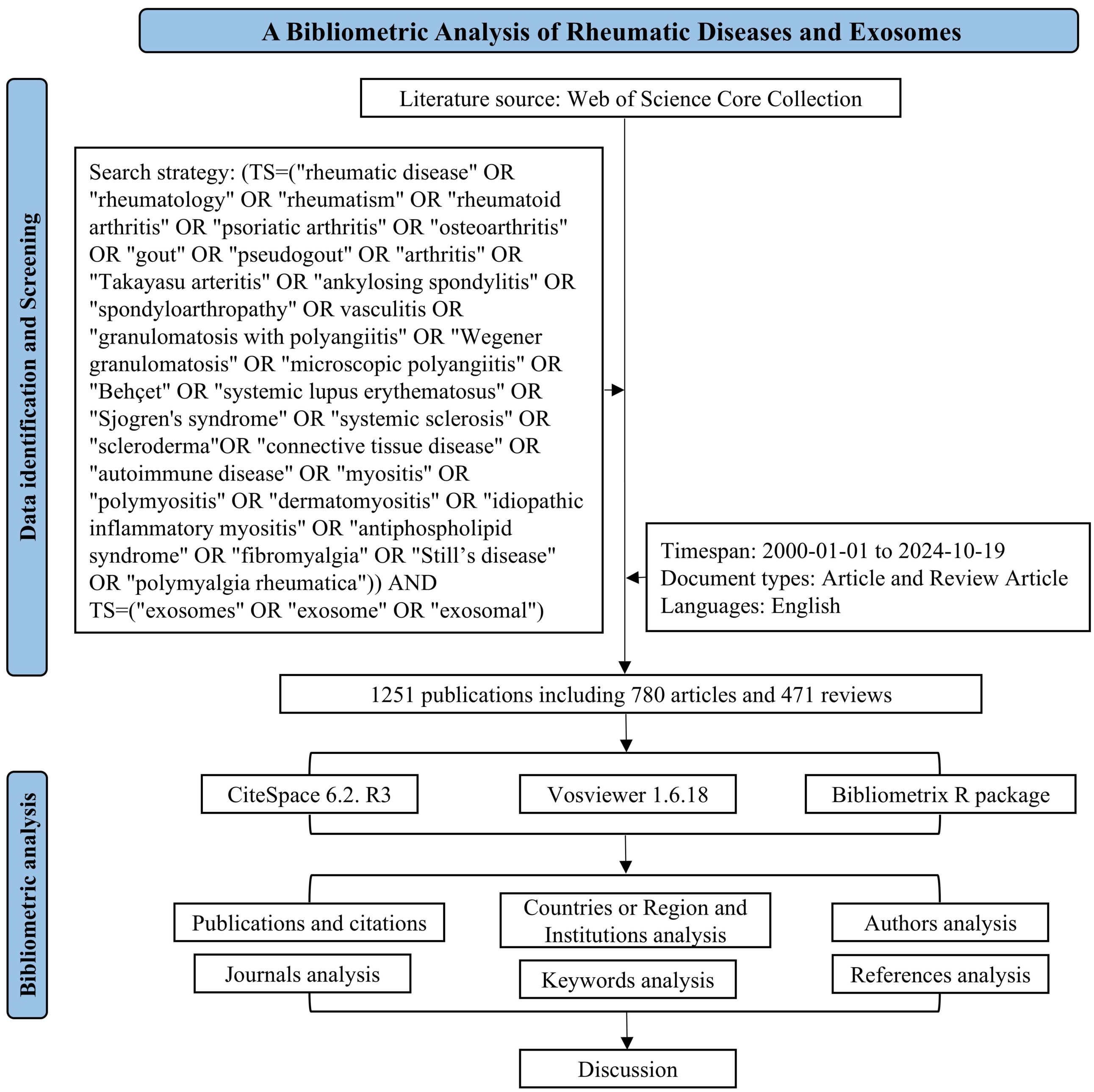

Figure 1 The flow chart for data extraction and analysis process.

Data Analysis and Visualization

We use CiteSpace 6.2. R3, VOSviewer 1.6.18, and Bibliometrix R packages to conduct data analysis and visualization of the countries or regions, institutions, authors, journals, keywords, and references involved in this field. CiteSpace is renowned for its ability to visualize citation networks, knowledge structures, research fronts, and trends in scientific domains.[21] Node size indicates relative proportion and line thickness shows connection strength.[22] It provides a range of metrics to assess the significance of nodes within a network. Temporal metrics like citation burst indicate periods of abrupt change in the frequency of an entity, highlighting emerging terms.[23] Structural metrics such as centrality, modularity, and silhouette score are used. Nodes with high centrality (≥ 0.1) generally connect different clusters and are quantitatively considered pivotal in network analysis. The modularity and silhouette metrics, namely the Q value and the S value, are important for assessment. Generally, the Q value ranges from 0 to 1, and the S value ranges from −1 to 1. Low Q value indicates fuzzy clusters, while high Q value indicates clear cluster structure. The Q value greater than 0.3 indicates the identified community structure is significant. The S value exceeding 0.7 considered high credibility and exceeding 0.5 considered reasonable. If the S value approaches 1, the cluster is perfectly separated from others. If the S value approaching 0 suggests ambiguous cluster boundaries, and approaching −1 suggests invalid partitioning.[24] VOSviewer is a software tool designed for creating and visualizing bibliometric networks. Node size indicates item frequency, line thickness represents the strength of association, and colors distinguish thematic clusters.[25] Bibliometrix is an R package designed for comprehensive science mapping analysis, providing a suite of tools for quantitative research in bibliometrics and scientometrics. This package supports three key phases of analysis: data importing and conversion to R format, bibliometric analysis of a publication dataset, and building and plotting matrices for co-citation, coupling, collaboration, and co-occurrence analysis.[26]

Results

Analysis of Publication Outputs and Growth Trend Predictions

Annual publications can reflect research progress and trends in the field. From 2000 to 2024, a total of 1,251 publications were extracted from WOSCC database, including 780 articles and 471 reviews. As of October 19, 2024, these articles received 49,374 citations, equating to an average of 39.47 citations per article. As shown in Figure 2, the overall publication trend has increased since the 21st century. In 2020, the number of papers grew rapidly, reaching 100 for the first time. Since then, there has been an exponential increase in the number of papers each year. Moreover, as

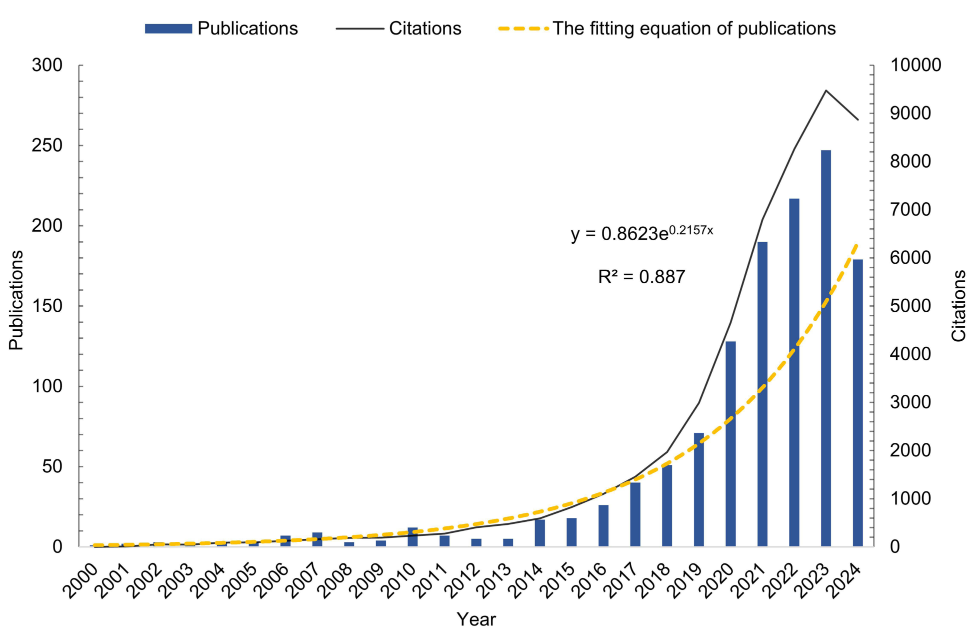

Figure 2 The annual publication, annual citation frequency, and the growth trend prediction.

demonstrated in Supplementary Figure 1, the dominance of research articles within this growth continues and even increases. Additionally, citation frequency has increased significantly. The fitting equation for publications was $y = 0.8623e^{0.2157x}$, and the simulation curve clearly indicates a relatively strong coefficient of determination (R^2 = 0.8987), which suggests that the number of annual articles is expected to steadily increase.

Analysis the Network of Cooperation Across Countries or Regions and Institutions

A total of 255 different countries or regions were extracted from our database. The top 10 countries with the highest number of publications and citations are reported in Table 1. China was the most productive country (n = 699, 55.88%), followed by the USA (n = 205, 16.39%), Italy (n = 67, 5.36%). Meanwhile, China has established a leading position in terms of citation frequency and H-index, indicating its significant contribution to the development of this field and its extremely high degree of influence. Figure 3A illustrates the collaborative network between countries or regions. Supplementary Table 1 shows the top three countries or regions with high centrality are the USA (0.45), Germany (0.22), and China (0.22). The burst intensity revealed that the USA had the biggest strength, and the longest citation burst (2000 to 2018, strength 23.66) (Supplementary Figure 2). These analysis highlight that the global research focus is primarily on the function of exosomes and potential therapeutic applications in RDs (like cartilage repair and regeneration).[27,30]

An analysis of 4,413 institutions shows that the primary research institutions in this field are primarily based in China. The visual analysis reveals that Shanghai Jiao Tong University holds significant influence in the field, which published 43 articles with 2,694 citations, with an average of 62.65 citations per article and an H-index of 19. Furthermore, although the Pennsylvania Commonwealth System of Higher Education published only 20 articles, with an average citation of 160.45, far surpassing the other institutions (Table 2). At the same time, Supplementary Table 1 indicates that it is also the institution with the highest centrality. Figure 3B demonstrated that network collaboration between institutions. Radboud University Nijmegen showed the strongest citation burst (2001 to 2007, strength 7.9) (Supplementary Figure 2).

Analysis the Network of Authors and Co-Citation Authors

Analyzing authors' contributions provides a straightforward means of identifying academic pioneers in the field. Using VOSviewer, we visualize an extensive analysis of 7,213 authors as shown in Figure 4. To enhance the clarity of the visualization, Figure 4A demonstrated a collaborative network analysis on a subset of 85 authors, each having at least 11 publications, ultimately forming 18 clusters. Cluster #1 (red) is the largest, comprising 11 items. Cluster #2 (green) forms a collaborative network centered around professors Liang Yujie, Duan Li, and Xu Xiao from Shenzhen University, who are also the top three contributors in terms of publication count. Their research emphasizes the role of exosomes as effective carriers for delivering miRNA into chondrocytes in osteoarthritis treatment.[31,35] Cluster #3 (blue) primarily consists of researchers hailing from IRCCS Institute Orthopedic Galeazzi, with De Girolamo, Laura as the central figure, and their primary research focus on adipose-derived mesenchymal stem cells (ASCs)-extracellular vehicles (EVs).[36,38]

Table 1 The Top 10 Countries or Regions of the Number of Publications and Frequency of Citations

Rank	Country or Region	Article Counts	Year	H-Index	Total Citations	Average Citations
1	China	699	2010	68	19,666	28.13
2	USA	205	2000	58	13,219	64.48
3	Italy	67	2001	26	3446	51.43
4	South Korea	57	2015	20	1931	33.88
5	Iran	47	2017	20	1245	26.49
6	Japan	42	2010	19	1259	29.98
7	Germany	38	2002	21	1569	41.29
8	England	33	2010	17	874	26.48
9	Spain	33	2004	18	1312	39.76
10	France	30	2001	18	3635	121.17

Note: Year means the first publication year recorded for the countries or regions.

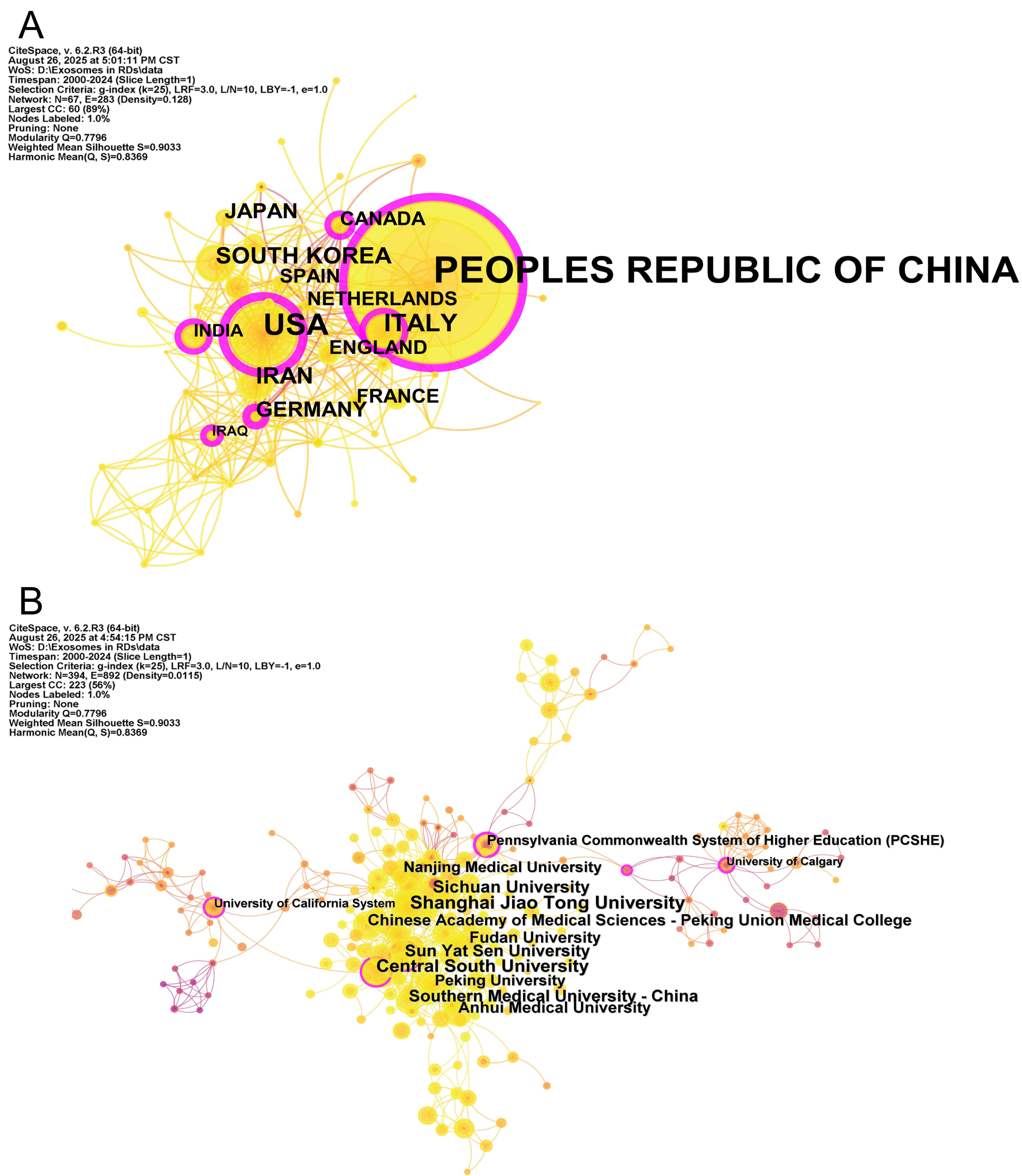

Figure 3 The network map of cooperation between countries or regions (**A**) and institutions (**B**).
Notes: Data for the "Taiwan" region is included within "People's Republic of China".

Cluster #4 (yellow) is centered on Toh Wei Seong from the National University of Singapore, who proposed MSCs exosomes could mediate M2-like macrophage polarization in the immunoregulatory mechanism.[39] Notably, Table 3 highlights Toh Wei Seong ranks 4th in publication count and is the only author in the top 10 by publication output who also ranks within the top 10 for citation frequency. It is evident that active cooperation occurs within the same cluster,

Table 2 The Top 10 Institutions of the Number of Publications and Frequency of Co-Citations

Rank	Institution	Article Counts	Year	H-Index	Total Citations	Average Citations	Country
1	Shanghai Jiao Tong University	42	2017	19	2694	62.65	China
2	Central South University	34	2013	18	1100	32.35	China
3	Sichuan University	31	2020	13	701	22.61	China
4	Sun Yat Sen University	28	2018	15	1244	42.90	China
5	Southern Medical University - China	26	2019	10	412	15.85	China
6	Fudan University	23	2020	9	342	14.87	China
7	Chinese Academy of Medical Sciences - Peking Union Medical College	23	2018	11	357	14.88	China
8	Anhui Medical University	22	2018	10	627	28.50	China
9	Peking University	21	2018	9	294	14.00	China
10	Nanjing Medical University	21	2010	14	839	39.95	China

Note: Year means the first publication year recorded for the institutions.

whereas cross-cluster collaboration is not discernible. Figure 4B demonstrates that Théry C is the most frequent co-citations author, with work indicating that exosomes possess a unique molecular composition and potent immunostimulatory properties,[29] followed by Zhang S, Tao S, and Cosenza S. The authors were primarily grouped into 4 clusters in the co-citation network, namely Théry C, Raposo G, Kim Sh, etc. from cluster #1 (red); Zhang Sp, Tao Sc, Cosenza S, Mao Gp, Toh Ws, etc. from cluster #2 (blue); Zhang Y, Kalluri R, etc. from cluster #3 (green); Lai Rc, etc. from cluster #4 (yellow). Cluster #1 (red) and cluster #2 (blue) focus on clinical research involving mesenchymal stem cells-derived exosomes for the prevention and treatment of inflammatory arthritis.[40,43]

Analysis of Journals, Co-Citation Journals, and Research Categories

To assess the impact and academic status of journals in this field, we performed a visual analysis of the journals. As shown in Table 4 and Figure 5A, the journal with the highest number of publications is Frontiers in Immunology (n = 63, 5.04%), followed by International Journal of Molecular Sciences (n = 54, 4.32%) and Stem Cell Research & Therapy (n = 30, 2.40%). Among the top 10 productive journals, there were 7 journals ranked in Q1 according to Journal Citation Reports (JCR), 5 of which had an impact factor (IF) higher than 5. The journal with the highest citation is Stem Cell Research & Therapy (n = 2248), followed by Journal of Immunology (n = 1691), and International Journal of Molecular

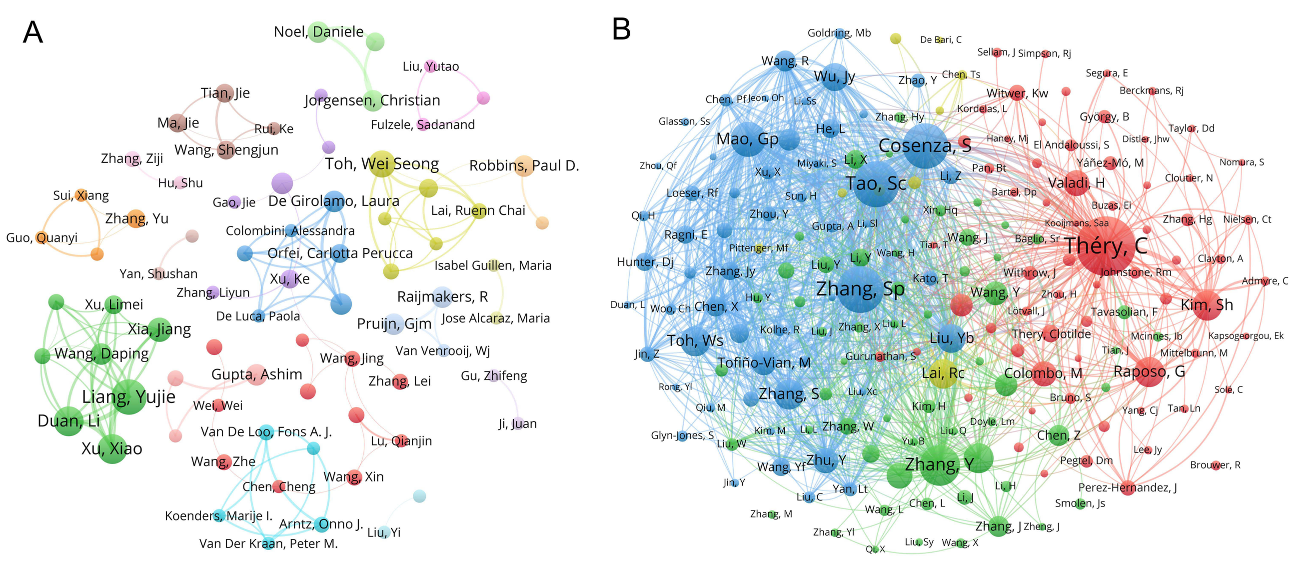

Figure 4 The visualization map of authors' co-authorship (**A**) and co-citation (**B**).

Table 3 The Top 10 Authors of the Number of Publications and Frequency of Co-Citations

Rank	Author	Article Counts	Citations	Total Link Strength	Rank	Author	Co-Citations	Total Link Strength
1	Liang, Yujie	13	714	53	1	Théry, C	400	7478
2	Duan, Li	11	688	50	2	Zhang, Sp	310	7204
3	Xu, Xiao	11	710	50	3	Tao, Sc	306	7838
4	Toh, Wei Seong	10	1482	30	4	Cosenza, S	298	7061
5	Xia, Jiang	9	645	31	5	Zhang, Y	262	5685
6	De Girolamo, Laura	8	168	31	6	Mao, Gp	225	6595
7	Gupta, Ashim	8	143	11	7	Kalluri, R	191	3531
8	Jorgensen, Christian	8	1148	15	8	Raposo, G	191	3632
9	Noel, Daniele	8	1148	15	9	Toh, Ws	188	3798
10	Pruijn, Gjm	8	405	12	10	Kim, Sh	187	3305

Table 4 The Top 10 Journals and Co-Cited Journal

Rank	Journal	Article Counts	H-Index	JCR (2025)	IF (2025)	Co-Cited Journal	Co-Citations	JCR (2025)	IF (2025)
1	Frontiers in Immunology	63	23	Q1	5.9	Stem Cell Research & Therapy	2248	Q1	7.3
2	International Journal of Molecular Sciences	54	16	Q1	4.9	Journal of Immunology	1691	Q2	3.4
3	Stem Cell Research & Therapy	30	19	Q1	7.3	International Journal of Molecular Sciences	1684	Q1	4.9
4	Journal of Nanobiotechnology	29	14	Q1	12.6	Frontiers in Immunology	1617	Q1	5.9
5	Frontiers in Bioengineering and Biotechnology	26	13	Q1	4.8	Scientific Reports	1536	Q1	3.9
6	Arthritis Research & Therapy	21	13	Q1	4.6	Osteoarthritis and Cartilage	1501	Q1	9.0
7	Cells	21	14	Q2	5.2	Plos One	1489	Q2	2.6
8	International Immunopharmacology	19	7	Q2	4.7	Journal of Extracellular Vesicles	1440	Q1	14.5
9	Frontiers in Cell and Developmental Biology	18	11	Q2	4.3	Biomaterials	1359	Q1	12.9
10	Autoimmunity Reviews	14	11	Q1	8.3	Arthritis Research & Therapy	1295	Q1	4.6

Sciences (n = 1684). Notably, the top three most productive journals also rank highly in terms of citation frequency, underscoring their significant academic influence, which may be attributed to their broad academic coverage. Additionally, we conducted an analysis of the top 20 research categories in this field, as depicted in Figure 5B. The primary research areas are focused on cell biology, immunology, experimental medicine research, biochemistry, and molecular biology. To explore the thematic distribution and citation trajectories of academic journals, we used a dual-map overlay of journals to highlight the extensive communication across interdisciplinary fields. This visual representation illustrates the citation connections between two distinct sections: the left side denotes the citing journals, while the right side denotes the cited journals. Figure 5C shows that journals within the realms of Molecular/ Biology/ Genetics are frequently cited by journals from Molecular/ Biology/ Immunology and Medicine/ Medical/ Clinical, illustrating the translation of basic research into clinical research.

Analysis of Co-Occurrence Keywords

A meticulous analysis of keywords was conducted to vividly identify the active research areas, the emerging trends, the development of new knowledge domains, and the relationships between different topics in this field. Figure 6A reveals a total of 372 nodes and 706 edges. The top three most prominent keywords are extracellular vesicles (n = 390), exosm (n = 316), and mesenchymal stem cells (n = 310), probably due to our search strategy. Exosomes are a subset of extracellular vesicles, but in many cases, the terms "exosomes" and "extracellular vesicles" are used interchangeably.[44] Exosomes derived from MSCs have garnered widespread attention due to their potential in tissue repair and regenerative

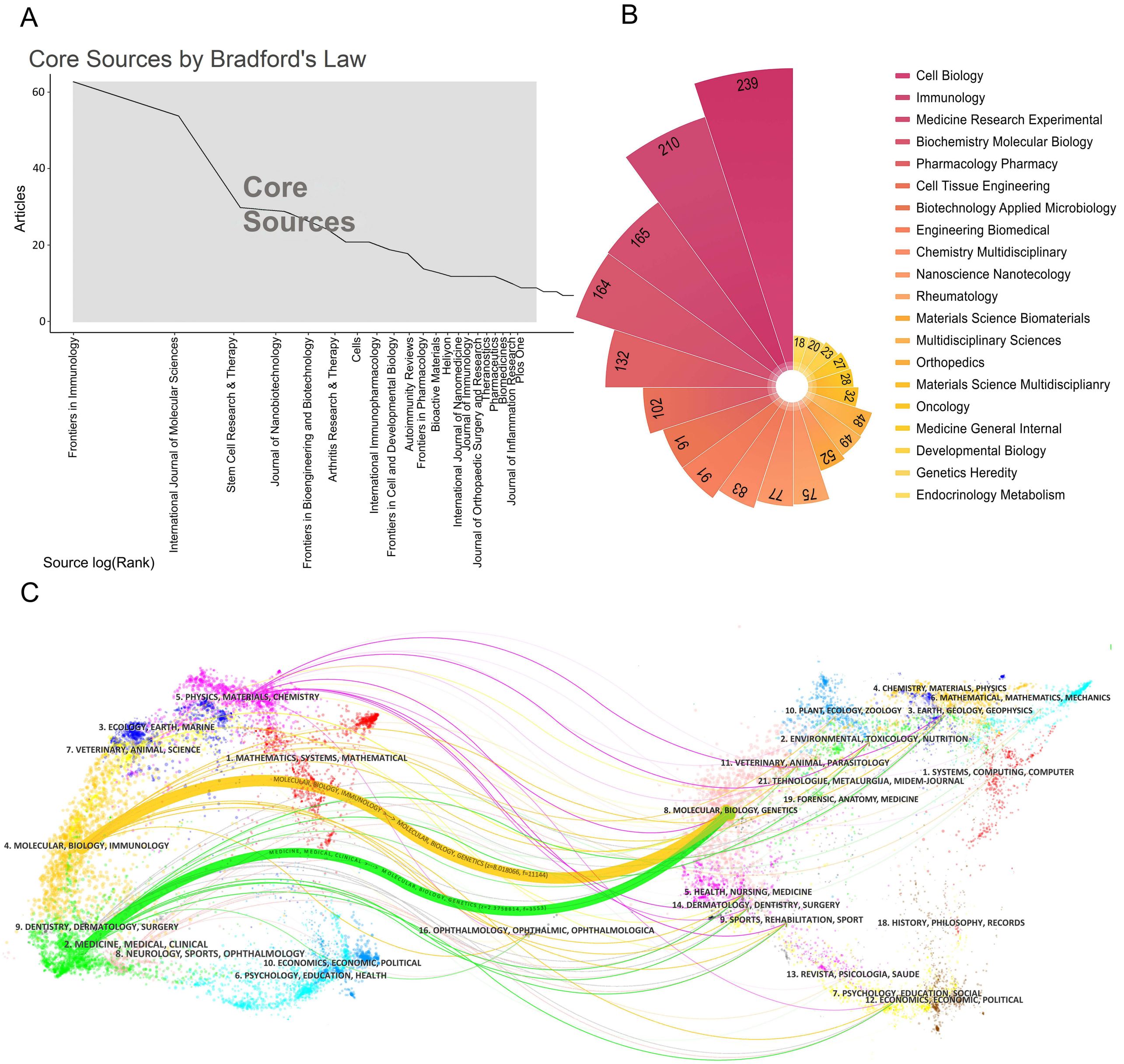

Figure 5 The analysis of journals, co-citation journals, and research categories. (**A**) Core Source Journals Identified by Bradford's Law. (**B**) Nightingale rose chart of the top 20 research categories. (**C**) A dual-map overlay of the journals.

medicine. The work of Zhang S is particularly representative. They discovered that exosomes from MSCs can promote cartilage regeneration through multiple mechanisms, including enhancing proliferation, reducing apoptosis, modulating immune responsiveness, and restoring matrix homeostasis.[30,43,45] Rheumatoid arthritis (n = 215) and osteoarthritis (n = 161) are the most extensively studied diseases. The keyword "expression" exhibits the highest centrality score of 0.54 within this network. Its high-cited articles indicate that exosomes from various sources, carrying specific molecular expressions such as miRNAs and proteins, have therapeutic potential in modulating pathological states and improving disease symptoms.[46,48] Supplementary Table 2, indicate that the keyword analysis also encompasses various laboratory indicators, including the pathological mechanisms of disease (such as inflammation),[49] construction of experimental models (such as collagen-induced arthritis models),[50,51] detection methods (such as in vitro or vivo experiments),[52] and indicators to assess therapeutic efficacy (such as vascular endothelial growth factor).[46] "Regeneration" is a key word widely used in clinical treatment. MSCs have been recognized as a rational therapeutic strategy in regenerative medicine.

Figure 6 The analysis of co-occurrence keywords. (**A**) The network visualization map of keywords. (**B**) The timeline view of keywords cluster.

However, compared with MSCs, exosomes derived from MSCs offer a more stable and controllable therapeutic entity. This innovative research direction has opened new avenues for the development of regenerative medicine.[53]

Keywords were classified into 13 clusters as shown in Figure 6B, including cluster #0 human pm scl, cluster #1 cancer, cluster #2 fas ligand, cluster #3 regenerative medicine, cluster #4 systemic sclerosis, cluster #5 chondrocytes, cluster #6 extracellular vesicles, cluster #7 expression, cluster #8 rheumatoid arthritis, cluster #9 dendritic cells, cluster

#10 mesenchymal stromal cells, cluster #11 mesenchymal stem cell, cluster #12 microparticle. The keyword cluster timeline boasted a modularity Q value of 0.7796 and a mean silhouette S value of 0.9033, which signifies a well-structured and interconnected field.[24] The timeline reveals a dynamic and evolving research field, with a clear progression from basic science to translational and therapeutic research. It highlights the multidisciplinary nature in this field, encompassing immunology, cell biology, and regenerative medicine, with a growing emphasis on the role of exosomes in disease pathogenesis and potential therapeutic applications. Supplementary Figure 3 showed the keyword citation burst analysis from 2000 to 2024. The keyword "dendritic cells" shows the strongest citation burst (2006 to 2018; strength 18.03). The keyword with the longest duration is "autoantibody" and "autoimmune disease" for lasting 14 years.

Therefore, we have made a systematic summary of the expression of exosomes in RDs, presented in Table 5 and Table 6, showing that exosomes are significantly expressed in specific RDs, particularly OA and RA. Current research is mainly conducted in animal models and other basic studies. The functions of exosomes vary depending on their source

Table 5 The in-Depth Impact of Exosomes Sourced From Various Types on OA

Exosome Source	Exosome Cargo	Model	Biological Effects	Study
MSCs	MiR-92a-3p	Mouse	Regulate cartilage development and homeostasis by inhibiting Wnt5a expression	[48]
	LncRNA-KLF3-AS1	Mouse	Induce chondrocyte proliferation and inhibit chondrocyte apoptosis via miR-206/GIT1 axis	[47]
	LncRNA-KLF3-AS1	Rat	Promote cartilage repair and chondrocyte proliferation	[54]
	N.D.	Mouse	Protect chondrocytes from apoptosis and inhibit macrophage activation	[55]
	N.D.	Mouse	Regulate the level of chondrocyte glutamine metabolism	[56]
	N.D.	Mouse	Rescue cartilage injury through the reduction of ferroptosis in macrophages via GOT1/CCR2/Nrf2/HO-1 signaling pathway	[57]
	N.D.	Rat	Attenuate inflammation and restore matrix homeostasis	[43]
	N.D.	Rabbit	Inhibit mitochondrial dysfunction-induced apoptosis of chondrocytes	[58]
BMSCs	MiR-206	Mouse	Promote osteoblast proliferation and differentiation by reducing ELF3	[59]
	MiR-136-5p	Mouse	Promote chondrocyte migration and inhibit chondrocyte degeneration by targeting ELF3	[60]
	MiR-125a-5p	Mouse	Induce chondrocyte migration and inhibit cartilage degeneration by downregulating E2F2	[61]
	MiR-9-5p	Rat	Alleviate inflammation and protect cartilage by inhibiting syndecan-1	[62]
	MiR-127-3p	Rat	Relieve chondrocyte damage by inhibiting cadherin 11-mediated Wnt/beta-catenin pathway	[63]
	MiR-361-5p	Rat	Alleviate chondrocyte damage by targeting DDX20 and inactivating the NF-κB pathway	[64]
	MiR-326	Rat	Inhibit pyroptosis of chondrocytes and cartilage by targeting HDAC3 and STAT1//NF-κB p65	[65]
	CircYAP1, miRNA-21	Rat	Mitigate OA symptoms and pathology progression through circYAP1/ miRNA-21/ TLR7 axis	[66]
	CircRNA_0001236	Mouse	Alleviate cartilage degradation and enhance cartilage repair through miR-3677-3p/Sox9 axis	[67]
	LncRNA MEG-3	Rat	Reduce the senescence and apoptosis of chondrocytes	[68]
	LncRNA SNHG7	Human chondrocytes	Inhibit inflammation and ferroptosis through miR-485-5p/FSP1 Axis	[69]
	LncRNA LYRM4-AS1	Chondrocytes	Regulate the lncRNA LYRM4-AS1-GRPR-miR-6515-5p to alleviate inflammation	[70]
	TGF-131	Mouse	Inhibit abnormal angiogenesis in subchondral bone	[71]
	Runx2	Rabbit	Promote the proliferation, migration, and phenotypic maintenance of articular chondrocytes	[72]
	N.D.	Mouse	Abrogate the aberrant nerve invasion in subchondral bone	[73]
	N.D.	Rat	Promote cartilage repair and ECM synthesis, and relieve pain	[74]
	N.D.	Rat	Promote the phenotypic transformation of synovial macrophages from M1 to M2	[75]
	N.D.	Rat	Inhibit chondrocyte apoptosis and the expression of MMPs, and regulate dynamin-related protein 1-mediated mitophagy	[76]
	N.D.	Rat	Attenuate chondrocyte ferroptosis by disrupting the METTL3-m6A-ACSL4 axis	[77]
	N.D.	Chondrocytes	Protect chondrocytes by inhibiting cell apoptosis and inflammatory response	[78]

(*Continued*)

Table 5 (Continued).

Exosome Source	Exosome Cargo	Model	Biological Effects	Study
UC-MSCs	MiRNAs	Rat	Promote chondrocyte proliferation and migration, inhibit chondrocyte apoptosis and regulate the polarization of macrophages	[79]
	MiR-100-5p	Human chondrocytes	Inhibit ROS production and cell apoptosis through the miR-100-5p/NADPH oxidase 4 axis	[80]
	MiRNAs	Human chondrocytes	Anti-inflammation by reversing COL2A1 and MMP13	[81]
	N.D.	Mouse	Anti-inflammation by reducing pro-inflammatory cytokines and increasing Arg-1 expression in macrophages and synovial fibroblasts	[82]
	N.D.	Rat	Promote cartilage regeneration by downregulating synovial fluid cytokines, MMP13 and ADAMTS-5, and upregulating COL2	[83]
WJMSCs	MiRNAs	Rabbit	Enhance the reparative effect of the acellular cartilage ECM scaffold by regulating the microenvironment of the articular cavity	[84]
SMSCs	MiR-155-5p	Mouse	Enhance proliferation and migration, attenuate apoptosis, and modulate ECM secretion in chondrocytes	[85]
	MiR-485-3p	Mouse	Relieve cartilage degradation by targeting neuropilin-1 and succedent inactivation of the PI3K/Akt pathway	[86]
	MiR-320c	Rat and human chondrocytes	Suppresse ECM degradation and chondrocyte apoptosis to enhance chondrogenesis by targeting ADAM19	[87,88]
	MiR-140-5p, Wnt5a, Wnt5b	Rat	Enhance the proliferation and migration without damaging ECM secretion	[41]
	MiR-129-5p	Human chondrocytes	Inhibite HMGB1 release	[89]
	MiR-212-5p	Human chondrocytes	Suppress chondrocyte degeneration and inflammation by targeting ELF3	[90]
	MATN3	Mouse	Prevent ECM degradation and autophagy defects by delivering MATN3/IL-17A	[52]
	BMP-7	Mouse	Attenuate inflammation and cartilage injury by synovial macrophages M2 polarization	[91]
ESC-MSCs	N.D.	Mouse	Balance synthesis and degradation of cartilage ECM	[92]
IPFP-MSCs	MiR-100-5p	Mouse	Protect articular cartilage and ameliorate gait abnormalities by inhibiting the mTOR-autophagy pathway	[49]
ADSCs	MiR-93-5p	Mouse	Inhibit inflammation and alleviate the progression of OA by targeting miR-93-5p/ ADAMTS9 signal axis	[93]
	miR-338-3p	Mouse	Inhibit Runx2 expression	[94]
	miR-486-5p	Rat	Alleviate endoplasmic reticulum stress induced chondrocyte apoptosis	[95]
	MiR-376c-3p	Rat	Mitigate chondrocyte degradation and synovial fibrosis through repress the Wnt-beta-catenin pathway by targeting Wnt3 or Wnt9a	[96]
	MiR-429	Rat	Ameliorate chondral injury via promote autophagy and chondrocyte proliferation by targeting FEZ2	[97]
	MiR-145, MiR-221	Chondrocytes	Promote chondrogenesis and suppress inflammation	[98]
USCs	MiR-140-5p	Rat	Enhance proliferation and migration, inhibit apoptosis and increase ECM secretion by downregulating VEGFA	[99]
	N.D.	Rat	Inhibit chondrocyte apoptosis and inflammation and promote chondrocyte proliferation, increase the structural integrity and smoothness of the cartilage surfaces	[100]
DPSCs	MiR-140-5p	Rat	Inhibit chondrocyte apoptosis by regulating the expression levels of apoptosis-related proteins	[101]
	N.D.	Mouse	Repress osteoclast activation by inhibiting TRPV4 activation	[102]
SHEDs	MiR-100-5p	Human chondrocytes	Suppress inflammation by repressing mTOR expression	[103]
	N.D.	Human chondrocytes	Suppress inflammation through the NF-κB pathway	[104]
CSPCs	N.D.	Rat	Promote cartilage repair by modulating immune responses, inhibiting inflammation, and improving the intracellular environment	[105]
SSCs	N.D.	Rat and rabbit	Promote meniscal healing in the avascular region through inflammation modulation, promotion of cell migration, and secretion of ECM components	[106]
SF	MiR-182	Rat and human chondrocytes	Participate in the dual variation of the OA microenvironment	[107]
	MiR-182-5p	Human chondrocytes	Downregulate TNFAIP8 and promote autophagy via the ATG/LC3 pathway	[108]

(*Continued*)

Table 5 (Continued).

Exosome Source	Exosome Cargo	Model	Biological Effects	Study
FLSs	MiR-146a	Rat	Modulate cartilage degradation and macrophage polarization through modulate the TLR 4/TRAF6/NF-κB pathway	[109]
	MiR-126-3p	Rat	Constrain chondrocyte inflammation and cartilage degeneration	[110]
	MiR-214-3p	Rat	Ameliorate chondrocyte inflammation and degeneration of cartilage tissues	[111]
	MiR-19b-3p	Rat and human chondrocytes	Enhance cartilage ferroptosis and damage by sponging SLC7A11	[112]
M2 macrophages	MiR-26b-5p	Mouse	Regulate macrophage polarization and chondrocyte hypertrophy by targeting TLR3 and COL10A1	[13]
	N.D.	Rat	Protect KOA by inhibiting the PI3K/AKT/mTOR Pathway	[113]
M1 macrophages	MiR-363	Human chondrocytes	Mediate the destructive effect of M1 macrophages on chondrocytes by repressing G3BP2	[114]
Vascular endothelial cells	N.D.	Mouse	Induce apoptosis via decrease the ability of chondrocytes to resist oxidative stress by inhibiting autophagy and p21 expression	[115]
Chondrocytes	MiR-95-5p	Human chondrocytes	Regulate cartilage development and homoeostasis via histone deacetylase 2/8[	[116]
	N.D.	Mouse	Restore mitochondrial dysfunction and polarize macrophage response toward an M2 phenotype	[117]
	N.D.	Rat	Accelerate cartilage calcification	[118]
Osteocytes	DLX2	Mouse	Mediate cartilage repair and inactivate the Wnt pathway	[119]
Osteoclasts	MiRNAs	Mouse	Decrease the resistance of cartilage to matrix degeneration, angiogenesis and sensory innervation	[120]
	MiR-212-3p	Mouse and human chondrocytes	Suppress the anabolism and accelerate the catabolism of chondrocytes by targeting TGF-beta 1/Smad2 signaling	[121]
Placenta	N.D.	Rat and human chondrocytes	Alleviate symptoms, suppress the expression of inflammatory and catabolic genes	[122]
Platelet	N.D.	Mouse	Promote chondrocyte proliferation and migration and attenuate cartilage degeneration to improve the microarchitecture of subchondral bone	[123]
PRP	N.D.	Rabbit	Protect articular cartilage and inhibit apoptosis via Wnt/β-catenin signaling pathway	[124]

Abbreviations: MSCs, Mesenchymal stem cells; BMSCs, Bone marrow MSCs; UC-MSCs, Umbilical cord MSCs; WJMSCs, Umbilical cord Wharton's jelly MSCs; SMSCs, Synovial MSCs; ESC-MSCs, Embryonic stem cell-induced MSCs; IPFP-MSCs, Infrapatellar fat pad MSCs; ADSCs, Adipose -derived MSCs; USCs, Urine-derived stem cells; DPSCs, Dental pulp stem cells; SHEDs, Stem cells from human exfoliated deciduous teeth; CSPCs, Primary chondrogenic stem cells; SSCs, Skeletal stem cells; SF, Synovial fluid; FLSs, Fibroblast-like synoviocytes; PRP, Platelet-rich plasma; GIT1, G-protein-coupled receptor kinase interacting protein-1; GOT1, Glutamic-oxaloacetic transaminase 1; CCR2, C-C motif chemokine receptor 2; Nrf2, Nuclear factor erythroid 2-related factor 2; HO-1, Heme oxygenase 1; Elf3, E74-like factor 3; E2F2, E2F transcription factor 2; DDX20, Asp-Glu-Ala-Asp-box polypeptide 20; HDAC3, Histone deacetylase 3; STAT1, Signal transducer and activator of transcription 1; YAP1, Yes-associated protein 1; TLR, Toll-like receptor; Sox9, Sex-determining region Y-box 9; SNHG7, Small nucleolar RNA host gene 7; FSP1, Ferroptosis suppressor protein 1; GRPR, Gastrin-releasing peptide receptor; TGF, Transforming growth factor; ECM, Extracellular matrix; METTL3, Methyltransferase like 3; M6A, N6-methyladenosine; ACSL4, Acyl-CoA synthetase long chain family member 4; ROS, Reactive oxygen species; COL2, Collagen type II; MMP, Matrix metalloproteinase; ADAMTS, A Disintegrin and metalloproteinase with Thrombospondin motifs; PI3K, Phosphatidylinositol 3-kinase; Akt, Protein kinase B; HMGB1, High mobility group protein-1; MATN3, Matrilin-3; BMP, Bone morphogenetic protein; FEZ2, Fasciculation and elongation protein zeta 2; VEGF, Vascular endothelial growth factor; TRPV4, Transient receptor potential vanilloid 4; TNFAIP, Tumor necrosis factor alpha-induced protein; ATG, Autophagy-related gene; LC3, Microtubule-associated protein 1A/1B-light chain 3; TRAF6, Tumor necrosis factor receptor-associated factor 6; SLC7A11, Solute carrier family 7 member 11; G3BP2, G3BP stress granule assembly factor 2; TGF-beta 1, Transforming Growth Factor-beta 1; Smad2, Mothers against decapentaplegic homolog 2.

Table 6 The in-Depth Impact of Exosomes Sourced From Various Types on RA

Exosome Source	Exosome Cargo	Model	Biological Effects	Study
MSCs	MiR-150-5p	Mouse	Inhibit synoviocyte hyperplasia and angiogenesis via MMP14 and VEGF	[46]
	CircFBXW7	Rat	Attenuate cell proliferation, migration and inflammation by targeting miR-216a-3p/HDAC4	[125]
	LncRNA HAND2-AS1	Human chondrocytes	Suppress the activation of RA-FLSs via miR-143-3p/TNFAIP3/NF-κB pathway	[126]
]BMSCs	MiR-205-5p	Mouse	Regulate MDM2 in FLSs	[127]
	MiR-23-5p	Mouse	Relieve inflammatory response	[128]
	MiR-223	Rat	Regulate the activation of inflammasomes via downregulation of NLRP3 expression in macrophages	[129]
	LncRNA TUG1	Mouse	Ameliorate RA damage via BLIMP1-mediated Th17/Treg balance	[130]
	Proteins	Rat	Alleviate RA symptoms through shuttling proteins related to cell adhesion and tissue repair ability	[131]
	FGL1	Rat	Suppress the inflammations, specific rheumatoid and immunological markers, meditate the NF-κB pathway to inhibit cell apoptosis	[132]

(*Continued*)

Table 6 (Continued).

Exosome Source	Exosome Cargo	Model	Biological Effects	Study
UC-MSCs	MiR-150-5p	Mouse	Alleviate bone erosion and regulate bone immunity via the aryl hydrocarbon receptor	[133]
	MiR-140-3p	Rat	Attenuate joint injury by silencing serum- and glucocorticoid-inducible kinase 1	[134]
	MiR-451a	Rat	Inhibit RA SFs proliferation, migration and invasion by inhibiting ATF2	[135]
	N.D.	Mouse	Regulate the balance between Th1/Th17 and Treg cells	[136]
SMSCs	CircEDIL3	Mouse	Ameliorate arthritis severity by targeting circEDIL3/miR-485-3p/PIAS3/STAT3/ VEGF functional module	[137]
GMSCs	N.D.	Mouse	Reduce incidences and bone erosion of arthritis by suppressing the immune response	[138]
FLSs	MiR-486-5p	Mouse	Induce osteoblast differentiation by activating the BMP/Smad signaling pathway and repressing Tob1	[139]
	MiR-106b	Mouse	Suppresses chondrocyte proliferation and migration by downregulating PDK4	[140]
	MiR-124-3p	Rat	Promote macrophage migration via PTX3 and PSMB5	[141]
	CircFTO	Mouse	Deteriorate RA by enhancing m6A modification of Sox9 in chondrocytes	[142]
	LncRNA HOTTIP	Mouse	Increase inflammation by targeting the miR-1908-5p/ STAT3 axis	[143]
	lncRNA TRAFD1-4:1	Human chondrocytes	Suppress chondrocyte proliferation and migration by degrading cartilage extracellular matrix	[11]
Macrophages	MiR-103a	Mouse	Promote inflammation and angiogenesis via the downregulation of HNF4 and activation of JAK/ STAT3 signaling pathway	[144]
PBMCs	LncRNA NEAT1	Mouse	Promote FLS proliferation and inflammation via the miR-23a/MDM2/SIRT6 axis	[145]

Abbreviations: GMSCs, Gingival MSCs; PBMSCs, Peripheral blood mononuclear cells; HDAC4, Histone deacetylase 4; MDM2, Murine double minute 2; NLRP3, NLR family pyrin domain-containing 3; BLIMP1, B lymphocyte-induced maturation protein 1; FGL1, Fibrinogen-like protein 1; ATF2, Activating transcription factor 2; PIAS3, Protein inhibitor of activated STAT3; PDK4, Pyruvate dehydrogenase kinase 4; PTX3, Pentraxin 3; PSMB5, Proteasome 20S subunit beta 5; TRAF1, Tumor necrosis factor-associated factor 1; HNF4A, Hepatocyte nuclear factor 4 alpha; JAK, Janus kinase; NEAT1, Nuclear paraspeckle assembly transcript 1; SIRT6, Sirtuin 6.

and the cargo they carry, with most exosomes originating from MSCs and expanding their functions beyond their inherent roles. Exosomes can carry a variety of cargoes, the most important of which are miRNAs, which regulate the expression of various protein-coding genes. The expression of exosomes in RDs involves multiple biological mechanisms and pathways, providing a basis for the development of new therapeutic strategies and potentially improving the treatment outcomes of RDs. These findings not only reveal the current research focus but also may provide significant insights into predicting the future development trends of the field.

Analysis of Co-Citation References

A co-citation analysis was conducted to elucidate the structural relationships among citations and to provide insights into the development trends and interdisciplinary connections within the field.[150] Table 7, extracted from the WoSCC database, presents a quantitative summary of the most influential research in the field. The number of citations range from 1,652 to 514, with most influential works originating from the USA. Figure 7A showed the most highly cited article is "Regulation of immune responses by extracellular vehicles" by Robbins, PD, published in 2014 in Nature Reviews Immunology (n = 1652). It provides an in-depth examination of the intricate mechanisms through which extracellular vesicles regulate immune responses. It underscores their potential as therapeutic targets or diagnostic markers in immunological disorders.[50] The second-ranked article is "Membrane vesicles, current state-of-the-art: emerging role of extracellular vesicles" by György, B (n = 1622), which emphasize the burgeoning role of extracellular vesicles in mechanisms of intercellular communication and immune regulation.[146] The main content of highly co-cited references emphasizes the powerful immunomodulatory functions of exosomes. In addition, exosomes also serve as potential biomarkers and therapeutic vehicles, with clinical applications in treating and preventing various inflammatory diseases. The article "Exosome: from internal vesicle of the multivesicular body to intercellular signaling device" by Denzer K has the highest centrality score of 0.32, as shown in Supplementary Table 3. The second ranking is the article "Exosome-mediated transfer of mRNAs and microRNAs is a novel mechanism of genetic exchange between cells" by Valadi H (0.31). They reveal the physiological functions and characteristics of exosomes. For instance, follicular dendritic cells

Table 7 The Top 10 Most Cited References

Rank	Article Title	First Author	Source	Time Cited	Country	Year
1	Regulation of immune responses by extracellular vesicles[50]	Robbins, PD	Nature Reviews Immunology	1652	USA	2014
2	Membrane vesicles, current state-of-the-art: emerging role of extracellular vesicles[146]	György, B	Cellular and Molecular Life Sciences	1622	Hungary	2011
3	Proteomic analysis of dendritic cell-derived exosomes: a secreted subcellular compartment distinct from apoptotic vesicles[29]	Théry, C	Journal of Immunology	1237	France	2001
4	Treatment of brain inflammatory diseases by delivering exosome encapsulated anti-inflammatory drugs from the nasal region to the brain[147]	Zhuang, XY	Molecular Therapy	1067	USA	2011
5	Immunoregulatory mechanisms of mesenchymal stem and stromal cells in inflammatory diseases[27]	Shi, YF	Nature Reviews Nephrology	742	China	2018
6	MSC exosomes mediate cartilage repair by enhancing proliferation, attenuating apoptosis and modulating immune reactivity[30]	Zhang, SP	Biomaterials	607	Singapore	2018
7	Exosomes from human saliva as a source of microRNA biomarkers[148]	Michael, A	Oral Diseases	552	USA	2010
8	Origins, structures, and functions of circulating DNA in oncology[149]	Thierry, AR	Cancer and Metastasis Reviews	548	France	2016
9	Emerging role of extracellular vesicles in inflammatory diseases[51]	Buzas, EI	Nature Reviews Rheumatology	536	Hungary	2014
10	Exosomes derived from miR-140-5p-overexpressing human synovial mesenchymal stem cells enhance cartilage tissue regeneration and prevent osteoarthritis of the knee in a rat model[41]	Tao, SC	Theranostics	514	China	2017

can bind to B-lymphocyte-derived exosomes on their cell surface.[151] Exosomes contain mRNAs and microRNAs. These RNAs can be delivered to other cells and translated into proteins within the recipient cells, facilitating the transfer of information between cells.[152] These articles are distributed across various journals, reflecting their relevance to immunology, oncology, rheumatology, regenerative medicine, and other disciplines.

The network shown in Figure 7 is pruned at a level that ensures the most significant connections, highlighting several key nodes and clusters that represent the central concepts and research foci within this domain, the modularity Q value of 0.7877 and a mean silhouette S value of 0.9095. Figure 7B identified 13 clusters, based on their content, these clusters were divided into two research directions. The first major research area encompasses RDs, represented by cluster #0 osteoarthritis, cluster #7 rheumatoid arthritis, and cluster #14 complications. Cluster #0, the largest cluster, focuses on the role of exosomes in promoting cartilage tissue regeneration and preventing osteoarthritis. The second principal research direction delves into the function and applications of exosomes in RDs. These clusters can be systematically categorized into three overarching groups: Molecular and cellular biology: cluster #2 reference genes, cluster #3 microparticles, cluster #9 microparticle, cluster #8 exocrine dysfunction, cluster #10 apoptotic bodies, and cluster #11 endosome; Immunology-related: cluster #1 autoimmunity, cluster #4 autoantibodies, cluster #12 toll-like receptor 4; Therapeutic applications: cluster #5 regeneration. The results of co-citation reference cluster align with the keyword analysis, revealing that research in this field is primarily concentrated on specific RDs. Research on exosomes spans multiple domains including genetics, cell biology, and molecular biology. In addition, the role of exosomes in immune responses and applications in regenerative medicine also shows great potential.

Discussion

In the 21st century (from 2000 to 2024), a total of 1251 publications and 49,374 citations related to RDs and exosomes were extracted from WOSCC database. The trend of annual publications and citations is expected to steadily increase. Notably, there was a rapid surge in the number of publications in 2020, which can be attributed to the widespread COVID-19 pandemic. This global health crisis has intensified the focus on autoimmune health,[153] as patients with rheumatic diseases are more susceptible to contracting COVID-19 compared to the general population.[154] The increased

Figure 7 The analysis of co-citation references. (**A**) The network visualization map of co-citation references. (**B**) The cluster visualization map of co-citation references.

dominance of research articles throughout the pandemic years is also notable It suggests that research in this area, potentially involving bioinformatics or experimental modeling, demonstrated resilience in the face of laboratory restrictions. However, additional factors, such as governmental healthcare policies, must also be considered in this context. Research on this topic spans 255 countries or regions and 4,413 institutions. China and the USA are leading contributors, with Chinese institutions such as Shanghai Jiao Tong University and Central South University dominating the number of publications. Based on the analysis of the authors and co-cited authors, Liang, Yujie is the most productive author, with the top three authors with the highest number of publications. Théry C stands out as the most frequently cited researcher. We have identified Frontiers in Immunology, International Journal of Molecular Sciences, Stem Cell Research & Therapy, and Journal of Immunology as the core journals in this field. The dual-map overlay of journals suggests that clinical medical research requires a foundation in experimental studies in molecular biology, biotechnology, and genetics.

Combining insights from the WOSCC database, the main research directions in this field focus on cell biology and immunology.

Through a detailed analysis of keywords and co-cited reference, the research focus and future development trends in the field during the 21st century can be discerned. As research progresses, the mysteries of exosomes are gradually being unveiled. Particularly, reference cluster analysis (such as cluster #3, cluster #8, cluster #9, and cluster #10) and co-citation reference centrality analysis both indicate that the composition, physiological characteristics, and applications of exosomes are the current focus of this field. Our research reveals that Théry C. is the most frequently cited author. As a leading figure in exosome research, she has revealed that exosomes play a crucial role in altering gene expression and intracellular signaling pathways in the recipient cells by transporting RNA, lipids, and proteins. Exosomes are captured by neighboring recipient cells through the interaction of vesicular ligands with cellular receptors, thereby participating in the transmission of biological signals and the regulation of various biological processes.[155,157] Each exosome is an extension of the characteristics and functions of its original cell. Exosomes function as vehicles for antigen presentation in immune responses, regulating the activation and signaling of immune cells.[152]

Keyword analysis revealed that "mesenchymal stem cells" exhibited a higher frequency of occurrence, and the top two keywords by centrality score were "expression" and "cell-derived exosomes", collectively indicating that research into MSC-derived exosomes is a current hotspot. Together with the results of the co-citation reference analysis (such as cluster #0 and cluster #7), recent studies demonstrate that in order to address the severe threat posed by RDs such as OA and RA, researchers are turning their attention to the potential of exosomes in disease diagnosis and treatment. Given the high prevalence and severe clinical outcomes of these diseases, inflammation and immune dysregulation are well-established pathogenic mechanisms. Exosomes can mediate disease progression and serve as therapeutic targets by participating in various pathological processes. As indicated by the dual-map overlay results, the knowledge trajectory in this field demonstrates a transition from basic research towards clinical research. Therefore, researchers have focused their attention on these diseases. Additionally, the availability of experimental models, accessibility of clinical samples, and substantial government funding are also key factors that have driven the research in this area.

The pathogenesis of OA is complex, with many pathological manifestations including synovial inflammation, ligament degeneration, subchondral bone remodeling, cartilage damage, and changes in the neuromuscular structures around the joints. The main factor leading to OA is a high level of inflammation. Inflammation plays a pivotal role in driving cartilage progression and bone destruction.[158] T lymphocytes and macrophages are the primary inflammatory cells involved in the pathogenesis of OA. Inflammatory fibroblast-like synoviocytes derived exosomes (FLS-exos) aggravate inflammation and M1 polarization in macrophage. Increased levels of the inflammatory response promote immune cell infiltration, proliferation, and angiogenesis, leading to further joint damage.[159] Synovial fluid-derived exosomes (SF-exos) contribute to the onset and progression of OA by promoting the activation of pro-inflammatory M1 macrophages and inducing the production of IL-1β along with other inflammatory cytokines. It also upregulated the levels of matrix metalloproteinase (MMP), leading to the degradation of the chondrocyte extracellular matrix (ECM).[160] Exosomes can modulate OA through their encapsulated cargo, such as miRNA and lncRNA. They may also serve as promising biomarkers, such as hsa_circ_0104873, which significantly increased in the SF of OA patients.[161]

RA is characterized by synovial hyperplasia, immune cell infiltration, and autoantibody production. The immune pathogenesis of RA is related to an imbalance between memory Th17 and memory regulatory T cells. As antigen-presenting carriers, exosomes in the SF of RA patients contain citrullinated proteins that are recognized by anti-citrullinated peptide antibodies, a hallmark of RA. This recognition initiates an inflammatory response characterized by the proliferation of Th1 and Th17 cells, ultimately leading to joint damage.[162] During the active phase of RA, plasma exosomes increase the release of pro-inflammatory cytokines such as IL-1, TNF, and IL-17.[163] Exosomes contribute to joint destruction and inflammatory processes: various nucleic acid components carried by exosomes, such as high levels of miR-221-3p and circFTO in FLS-exos, can damage bone and cartilage.[142,164] The lncRNA in exosomes can activate the NF-κB and Wnt signaling pathways, leading to Th17/Treg centered inflammation and resulting in synovial cells damage.[165] On the other hand, exosomes derived from inflammatory FLS can induce macrophages M1 polarization, generating a pro-inflammatory response.[166] Additionally, studies have shown that exosomes from RA patients carrying the co-inhibitory receptor PD-1 and related miRNAs can induce T cell exhaustion, leading to the progression of RA into a chronic disease.[167] Furthermore, circulating exosomal miRNA and serum exosomal lncRNA may be valuable biomarkers for RA.[168,170]

Exosomes are double-edged swords in biological processes. While implicated in the pathogenesis of RDs, they also hold significant therapeutic potential. Exosomes from diverse sources, carrying various cargos, exhibit distinct therapeutic effects on RDs. MSCs have been widely used as immunosuppressants and are emerging as a research hotspot in regenerative medicine. Studies have demonstrated that MSC-Exos possess anti-apoptotic, anti-inflammatory, and regenerative effects in RDs.[171] MSC-exos can rescue cartilage injury and regulate macrophage polarization by reducing ferroptosis, a form of iron-dependent cell death implicated in OA.[57,141] Exosomes can promote cartilage regeneration and mitigate cartilage degradation. Synovial MSCs derived exosomes (SMSC-exos) regulate bone regeneration and significantly promote cartilage repair through the Wnt5a/Wnt5b/YAP pathway.[41] BMSC-Exos inherit the anti-inflammatory property of BMSCs, inhibiting macrophage activation reducing IL-1β levels and alleviating chondrocyte apoptosis.[55] Furthermore, Platelet-rich plasma derived exosomes (PRP-exos) can activate the Wnt/β-catenin signaling pathway, reduce pro-inflammatory factor IL-1β levels, and alleviate joint t inflammation.[124] FLS from RA patients exhibit an aggressive phenotype that causes damage to cartilage and bone.[172] Components such as Fibrinogen-like protein 1 (FGL1) and miR-143-3p contained in MSC-exos can inhibit RA-FLS activation by reducing the activity of the NF-κB pathway.[126,132] Additionally, SMSC-exos inhibit signal transducer and activator of transcription 1 (STAT3) activity and downregulate vascular endothelial growth factor (VEGF) complex expression, resulting in reduced angiogenesis.[137] BMSC-exos have also been shown to exert anti-inflammatory effects by dose-dependently inhibiting T lymphocyte proliferation and reducing the CD4+ and CD8+ T cell ratio.[173] It also ameliorates inflammation by preventing the release of NLRP3 (NLR family pyrin domain-containing 3) in RA rats.[129] UMSC-exos have demonstrated the ability to reduce the Th1/Th17 to Treg cell ratio.[136]

However, despite the potential applications of exosomes in RDs, several challenges that need to be addressed. Standardization and validation of products are major challenges. Current isolation techniques, such as ultracentrifugation, and the purity of exosomes produced by different methods, may affect the quality and efficacy of exosomes.[174] Exosomes can modulate the activity of recipient cells and therefore have potential immunogenicity and tumorigenicity. However, compared to MSCs, exosomes, as cell-free vesicles, significantly reduce immunogenicity.[175] Moreover, Heterogeneity in exosome yield and cargo composition between different batches and cell sources further complicates their clinical application. The keyword analysis timeline shows that the popularity of regenerative medicine research has increased significantly in recent years. Regenerative medicine is poised to emerge as the next frontier in this field, with the potential to lead to significant breakthroughs in the treatment of RDs. One promising therapeutic strategy is the bioengineering of exosomes, which exhibit enhanced targeting, retention and stability.[176] For example, engineered exosomes surface-modified with a chondrocyte-affinity peptide (CAP) and loaded with nuclear factor E2-related factor 2 (Nrf2) facilitated targeted delivery to cartilaginous endplate cells by inhibiting dynamin-related protein 1 (Drp1)-mediated mitochondrial fission.[177] Another innovative approach indicates that engineered exosomes loaded with triptolide can inhibit RA fibroblast proliferation and demonstrate lesion-targeting specificity, enhancing therapeutic efficacy.[178] In addition, pH-responsive engineered exosome can reprogram chondrocytes to sustainably produce endogenous hyaluronic acid (HA), enhancing cartilage regeneration.[179] To further optimize delivery efficiency, encapsulating exosomes into biomaterials like hydrogels enhances bioavailability and enables spatiotemporally controlled release, promoting cartilage protection and regeneration.[180,181] Superoxide dismutase 3 (SOD3)-rich exosome-loaded hydrogel microspheres reduce reactive oxygen species (ROS) and enhance ECM synthesis in OA.[182] Moreover, magnetic polysaccharide hydrogel microcarriers co-deliver stem cell exosomes and diclofenac sodium to repair cartilage and alleviate OA symptoms.[183]

Bibliometrics analysis is a valuable tool for assessing academic impact and identifying trends, but it also has its limitations. Firstly, bibliometric indicators represent only one aspect of research evaluation and do not provide a comprehensive overview of research results. Secondly, bibliometrics methods may not always accurately capture emerging and interdisciplinary fields, as the body of literature is constantly evolving, and it often takes time for progress to be reflected in the data. Thirdly, relying solely on the WOSCC database for data collection may limit the interpretation of the results. However, most databases, such as PubMed, do not always provide complete references and citations for articles. Fourthly, the presence of homonymous authors could introduce errors in the author analysis, affecting the accuracy of the results. Finally, the language of the included literature is limited to English and the article types are restricted to articles and review articles, potentially excluding important articles. However, this limitation is inherent in the software used for the analysis.

Conclusion

In conclusion, this bibliometric analysis provides a comprehensive landscape of exosomes in RDs in the 21st century. The steady upward trend in publications and citations reflects the growing interest in the field. China and the USA emerge as prominent contributors. Théry C is the most frequently co-cited author and has a significant impact. Core journals like Frontiers in Immunology, International Journal of Molecular Sciences, and Stem Cell Research & Therapy suggest that the primary research foci are rooted in cell biology, immunology, and experimental medicine. This study highlights the dual role of exosomes in disease pathogenesis and treatment. The burgeoning interest in exosomes as key players in the progression of OA and RA, with the potential to serve as biomarkers and therapeutic vehicles, such as modulating immune dysregulation, cartilage degradation, and inflammatory responses. It also bridges basic science with clinical applications, providing a basis for regenerative medicine applications, such as engineering exosomes. Therefore, our analysis may foster the development of the field and help scholars to navigate the intellectual architecture of research frontiers of exosomes in RDs. Compared with other diseases, the research on the pathogenesis and therapeutic strategies of exosomes in RDs is relatively limited. Further studies are still required to elucidate the exact mechanisms of exosomes in RDs, which will provide novel insights for disease diagnosis and treatment.

Ethics Approval and Informed Consent

The manuscript does not contain clinical studies or patient data. The data were obtained directly from the database without any additional human or experimental animal involvement, so there was no need for ethical approval.

Author Contributions

Jing Luo and Qingwen Tao contributed equally and shared corresponding authorship. 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 known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

1. Ludwig AK, Giebel B. Exosomes: small vesicles participating in intercellular communication. *Int J Biochem Cell Biol*. 2012;44(1):11–15. doi:10.1016/j.biocel.2011.10.005
2. Xu L, Wu LF, Deng FY. Exosome: an Emerging Source of Biomarkers for Human Diseases. *Curr Mol Med*. 2019;19(6):387–394. doi:10.2174/1566524019666190429144310
3. Lee YJ, Shin KJ, Chae YC. Regulation of cargo selection in exosome biogenesis and its biomedical applications in cancer. *Exp Mol Med*. 2024;56(4):877–889. doi:10.1038/s12276-024-01209-y
4. Kalluri R, LeBleu VS. The biology, function, and biomedical applications of exosomes. *Science*. 2020;367(6478):eaau6977. doi:10.1126/science.aau6977
5. Samanta S, Rajasingh S, Drosos N, et al. Exosomes: new molecular targets of diseases. *Acta Pharmacol Sin*. 2018;39(4):501–513. doi:10.1038/aps.2017.162

6. Liang Y, Duan L, Lu J, et al. Engineering exosomes for targeted drug delivery. *Theranostics*. 2021;11(7):3183–3195. doi:10.7150/thno.52570
7. Zou Z, Li H, Xu G, et al. Current Knowledge and Future Perspectives of Exosomes as Nanocarriers in Diagnosis and Treatment of Diseases. *Int J Nanomedicine*. 2023;18:4751–4778. doi:10.2147/IJN.S417422
8. Koo M, Lu MC. Rheumatic Diseases: new Progress in Clinical Research and Pathogenesis. *Medicina (Kaunas)*. 2023;59(9):1581. doi:10.3390/medicina59091581
9. Badii M, Gaal O, Popp RA, et al. Trained immunity and inflammation in rheumatic diseases. *Joint Bone Spine*. 2022;89(4):105364. doi:10.1016/j.jbspin.2022.105364
10. Simoes D, Araujo FA, Monjardino T, et al. The population impact of rheumatic and musculoskeletal diseases in relation to other non-communicable disorders: comparing two estimation approaches. *Rheumatol Int*. 2018;38(5):905–915. doi:10.1007/s00296-018-3990-8
11. Ren J, Zhang F, Zhu S, et al. Exosomal long non-coding RNA TRAFD1-4:1 derived from fibroblast-like synoviocytes suppresses chondrocyte proliferation and migration by degrading cartilage extracellular matrix in rheumatoid arthritis. *Exp Cell Res*. 2023;422(2):113441. doi:10.1016/j.yexcr.2022.113441
12. Rodríguez-Muguruza S, Altuna-Coy A, Castro-Oreiro S, et al. A Serum Biomarker Panel of exomiR-451a, exomiR-25-3p and Soluble TWEAK for Early Diagnosis of Rheumatoid Arthritis. *Front Immunol*. 2021;12:790880. doi:10.3389/fimmu.2021.790880
13. Qian Y, Chu G, Zhang L, et al. M2 macrophage-derived exosomal miR-26b-5p regulates macrophage polarization and chondrocyte hypertrophy by targeting TLR3 and COL10A1 to alleviate osteoarthritis. *J Nanobiotechnology*. 2024;22(1):72. doi:10.1186/s12951-024-02336-4
14. Tavasolian F, Moghaddam AS, Rohani F, et al. Exosomes: effectual players in rheumatoid arthritis. *Autoimmun Rev*. 2020;19(6):102511. doi:10.1016/j.autrev.2020.102511
15. Chen X, Su C, Wei Q, et al. Exosomes Derived from Human Umbilical Cord Mesenchymal Stem Cells Alleviate Diffuse Alveolar Hemorrhage Associated with Systemic Lupus Erythematosus in Mice by Promoting M2 Macrophage Polarization via the microRNA-146a-5p/NOTCH1 Axis. *Immunol Invest*. 2022;51(7):1975–1993. doi:10.1080/08820139.2022.2090261
16. Miron RJ, Estrin NE, Sculean A, et al. Understanding exosomes: part 2-Emerging leaders in regenerative medicine. *Periodontol 2000*. 2024;94(1):257–414. doi:10.1111/prd.12561
17. Li W, Chen J, Zhao S, et al. High drug-loaded microspheres enabled by controlled in-droplet precipitation promote functional recovery after spinal cord injury. *Nat Commun*. 2022;13(1):1262. doi:10.1038/s41467-022-28787-7
18. Chen M, Wang Q, Wang Y, et al. Biomaterials-assisted exosomes therapy in osteoarthritis. *Biomed Mater*. 2022;17(2):022001. doi:10.1088/1748-605X/ac4c8c
19. Ji Y, Mi L, Zhao M, et al. Innovative Diagnosis and Therapeutic Modalities: engineered Exosomes in Autoimmune Disease. *Int J Nanomedicine*. 2024;19:3943–3956. doi:10.2147/IJN.S452184
20. Liu Y, Huang K, Zhou SL, et al. Engineered exosomal miR140 modulates mitophagy of chondrocytes through targeting CAPN1 to alleviate osteoarthritis. *Sci China Life Sci*. 2025;68(9):2617–2634. doi:10.1007/s11427-024-2843-7
21. Chen CM. CiteSpace II: detecting and visualizing emerging trends and transient patterns in scientific literature. *J Am Soc Inf Sci Tec*. 2006;57(3):359–377. doi:10.1002/asi.20317
22. Zhao Y, Chen GY, Fang M. Research Trends of Rheumatoid Arthritis and Depression from 2019 to 2023: a Bibliometric Analysis. *J Multidiscip Healthc*. 2024;17:4465–4474. doi:10.2147/JMDH.S478748
23. Wauthier L, Di CL, Favresse J. Sigma metrics in laboratory medicine: a call for harmonization. *Clin Chim Acta*. 2022;532:13–20. doi:10.1016/j.cca.2022.05.012
24. Chen C, Ibekwe-SanJuan F, Hou J. The Structure and Dynamics of Co-Citation Clusters: a Multiple-Perspective Co-Citation Analysis. *Journal of the American Society for Information and Technology*. 2010;61(7):1386–1409. doi:10.1002/asi.21309
25. van Eck NJ, Waltman L. Software survey: vOSviewer, a computer program for bibliometric mapping. *Scientometrics*. 2010;84(2):523–538. doi:10.1007/s11192-009-0146-3
26. Aria M, Cuccurullo C. bibliometrix: an R-tool for comprehensive science mapping analysis. *Journal of Informetrics*. 2017;11(4):959–975. doi:10.1016/j.joi.2017.08.007
27. Shi Y, Wang Y, Li Q, et al. Immunoregulatory mechanisms of mesenchymal stem and stromal cells in inflammatory diseases. *Nat Rev Nephrol*. 2018;14(8):493–507. doi:10.1038/s41581-018-0023-5
28. Skriner K, Adolph K, Jungblut PR, et al. Association of citrullinated proteins with synovial exosomes. *Arthritis Rheum*. 2006;54(12):3809–3814. doi:10.1002/art.22276
29. Théry C, Boussac M, Véron P, et al. Proteomic analysis of dendritic cell-derived exosomes: a secreted subcellular compartment distinct from apoptotic vesicles. *J Immunol*. 2001;166(12):7309–7318. doi:10.4049/jimmunol.166.12.7309
30. Zhang S, Chuah SJ, Lai RC, et al. MSC exosomes mediate cartilage repair by enhancing proliferation, attenuating apoptosis and modulating immune reactivity. *Biomaterials*. 2018;156:16–27. doi:10.1016/j.biomaterials.2017.11.028
31. Duan L, Liang Y, Xu X, et al. Recent progress on the role of miR-140 in cartilage matrix remodelling and its implications for osteoarthritis treatment. *Arthritis Res Ther*. 2020;22(1):194. doi:10.1186/s13075-020-02290-0
32. Liang Y, Xu X, Li X, et al. Chondrocyte-Targeted MicroRNA Delivery by Engineered Exosomes toward a Cell-Free Osteoarthritis Therapy. *ACS Appl Mater Interfaces*. 2020;12(33):36938–36947. doi:10.1021/acsami.0c10458
33. Liang Y, Xu X, Xu L, et al. Chondrocyte-specific genomic editing enabled by hybrid exosomes for osteoarthritis treatment. *Theranostics*. 2022;12(11):4866–4878. doi:10.7150/thno.69368
34. Liang Y, Xu X, Xu L, et al. Non-surgical osteoarthritis therapy, intra-articular drug delivery towards clinical applications. *J Drug Targeting*. 2021;29(6):609–616. doi:10.1080/1061186X.2020.1870231
35. Xu X, Liang Y, Li X, et al. Exosome-mediated delivery of kartogenin for chondrogenesis of synovial fluid-derived mesenchymal stem cells and cartilage regeneration. *Biomaterials*. 2021;269:120539. doi:10.1016/j.biomaterials.2020.120539
36. Ragni E, De Luca P, Perucca Orfei C, et al. Insights into Inflammatory Priming of Adipose-Derived Mesenchymal Stem Cells: validation of Extracellular Vesicles-Embedded miRNA Reference Genes as A Crucial Step for Donor Selection. *Cells*. 2019;8(4):369. doi:10.3390/cells8040369
37. Ragni E, Perucca Orfei C, De Luca P, et al. Identification of miRNA Reference Genes in Extracellular Vesicles from Adipose Derived Mesenchymal Stem Cells for Studying Osteoarthritis. *Int J Mol Sci*. 2019;20(5):1108. doi:10.3390/ijms20051108

38. Ragni E, Perucca Orfei C, De Luca P, et al. Interaction with hyaluronan matrix and miRNA cargo as contributors for in vitro potential of mesenchymal stem cell-derived extracellular vesicles in a model of human osteoarthritic synoviocytes. *Stem Cell Res Ther*. 2019;10(1):109. doi:10.1186/s13287-019-1215-z
39. Teo KYW, Zhang S, Loh JT, et al. Mesenchymal Stromal Cell Exosomes Mediate M2-like Macrophage Polarization through CD73/Ecto-5'-Nucleotidase Activity. *Pharmaceutics*. 2023;15(5):1489. doi:10.3390/pharmaceutics15051489
40. Cosenza S, Toupet K, Maumus M, et al. Mesenchymal stem cells-derived exosomes are more immunosuppressive than microparticles in inflammatory arthritis. *Theranostics*. 2018;8(5):1399–1410. doi:10.7150/thno.21072
41. Tao SC, Yuan T, Zhang YL, et al. Exosomes derived from miR-140-5p-overexpressing human synovial mesenchymal stem cells enhance cartilage tissue regeneration and prevent osteoarthritis of the knee in a rat model. *Theranostics*. 2017;7(1):180–195. doi:10.7150/thno.17133
42. Toh WS, Lai RC, Hui JHP, et al. MSC exosome as a cell-free MSC therapy for cartilage regeneration: implications for osteoarthritis treatment. *Semin Cell Dev Biol*. 2017;67:56–64. doi:10.1016/j.semcdb.2016.11.008
43. Zhang S, Teo KYW, Chuah SJ, et al. MSC exosomes alleviate temporomandibular joint osteoarthritis by attenuating inflammation and restoring matrix homeostasis. *Biomaterials*. 2019;200:35–47. doi:10.1016/j.biomaterials.2019.02.006
44. Welsh JA, Goberdhan DCI, O'Driscoll L, et al. Minimal information for studies of extracellular vesicles (MISEV2023): from basic to advanced approaches. *J Extracell Vesicles*. 2024;13(2):e12404. doi:10.1002/jev2.12404
45. Zhang S, Chu WC, Lai RC, et al. Exosomes derived from human embryonic mesenchymal stem cells promote osteochondral regeneration. *Osteoarthritis Cartilage*. 2016;24(12):2135–2140. doi:10.1016/j.joca.2016.06.022
46. Chen Z, Wang H, Xia Y, et al. Therapeutic Potential of Mesenchymal Cell-Derived miRNA-150-5p-Expressing Exosomes in Rheumatoid Arthritis Mediated by the Modulation of MMP14 and VEGF. *J Immunol*. 2018;201(8):2472–2482. doi:10.4049/jimmunol.1800304
47. Liu Y, Lin L, Zou R, et al. MSC-derived exosomes promote proliferation and inhibit apoptosis of chondrocytes via lncRNA-KLF3-AS1/miR-206/GIT1 axis in osteoarthritis. *Cell Cycle*. 2018;17(21–22):2411–2422. doi:10.1080/15384101.2018.1526603
48. Mao G, Zhang Z, Hu S, et al. Exosomes derived from miR-92a-3p-overexpressing human mesenchymal stem cells enhance chondrogenesis and suppress cartilage degradation via targeting WNT5A. *Stem Cell Res Ther*. 2018;9(1):247. doi:10.1186/s13287-018-1004-0
49. Wu J, Kuang L, Chen C, et al. miR-100-5p-abundant exosomes derived from infrapatellar fat pad MSCs protect articular cartilage and ameliorate gait abnormalities via inhibition of mTOR in osteoarthritis. *Biomaterials*. 2019;206:87–100. doi:10.1016/j.biomaterials.2019.03.022
50. Robbins PD, Morelli AE. Regulation of immune responses by extracellular vesicles. *Nat Rev Immunol*. 2014;14(3):195–208. doi:10.1038/nri3622
51. Buzas EI, György B, Nagy G, et al. Emerging role of extracellular vesicles in inflammatory diseases. *Nat Rev Rheumatol*. 2014;10(6):356–364. doi:10.1038/nrrheum.2014.19
52. Long L, Zou G, Cheng Y, et al. MATN3 delivered by exosome from synovial mesenchymal stem cells relieves knee osteoarthritis: evidence from in vitro and in vivo studies. *J Orthop Translat*. 2023;41:20–32. doi:10.1016/j.jot.2023.06.003
53. Moghadasi S, Elveny M, Rahman HS, et al. RETRACTED ARTICLE: a paradigm shift in cell-free approach: the emerging role of MSCs-derived exosomes in regenerative medicine. *J Transl Med*. 2021;19(1):302. doi:10.1186/s12967-021-02980-6
54. Liu Y, Zou R, Wang Z, et al. Exosomal KLF3-AS1 from hMSCs promoted cartilage repair and chondrocyte proliferation in osteoarthritis. *Biochem J*. 2018;475(22):3629–3638. doi:10.1042/BCJ20180675
55. Cosenza S, Ruiz M, Toupet K, et al. Mesenchymal stem cells derived exosomes and microparticles protect cartilage and bone from degradation in osteoarthritis. *Sci Rep*. 2017;7(1):16214. doi:10.1038/s41598-017-15376-8
56. Jiang K, Jiang T, Chen Y, et al. Mesenchymal Stem Cell-Derived Exosomes Modulate Chondrocyte Glutamine Metabolism to Alleviate Osteoarthritis Progression. *Mediators Inflamm*. 2021;2021:2979124. doi:10.1155/2021/2979124
57. Peng S, Sun C, Lai C, et al. Exosomes derived from mesenchymal stem cells rescue cartilage injury in osteoarthritis through Ferroptosis by GOT1/CCR2 expression. *Int Immunopharmacol*. 2023;122:110566. doi:10.1016/j.intimp.2023.110566
58. Qi H, Liu DP, Xiao DW, et al. Exosomes derived from mesenchymal stem cells inhibit mitochondrial dysfunction-induced apoptosis of chondrocytes via p38, ERK, and Akt pathways. *Vitro Cell Dev Biol Anim*. 2019;55(3):203–210. doi:10.1007/s11626-019-00330-x
59. Huang Y, Zhang X, Zhan J, et al. Bone marrow mesenchymal stem cell-derived exosomal miR-206 promotes osteoblast proliferation and differentiation in osteoarthritis by reducing Elf3. *J Cell Mol Med*. 2021;25(16):7734–7745. doi:10.1111/jcmm.16654
60. Chen X, Shi Y, Xue P, et al. Mesenchymal stem cell-derived exosomal microRNA-136-5p inhibits chondrocyte degeneration in traumatic osteoarthritis by targeting ELF3. *Arthritis Res Ther*. 2020;22(1):256. doi:10.1186/s13075-020-02325-6
61. Xia Q, Wang Q, Lin F, et al. miR-125a-5p-abundant exosomes derived from mesenchymal stem cells suppress chondrocyte degeneration via targeting E2F2 in traumatic osteoarthritis. *Bioengineered*. 2021;12(2):11225–11238. doi:10.1080/21655979.2021.1995580
62. Jin Z, Ren J, Qi S. Exosomal miR-9-5p secreted by bone marrow-derived mesenchymal stem cells alleviates osteoarthritis by inhibiting syndecan-1. *Cell Tissue Res*. 2020;381(1):99–114. doi:10.1007/s00441-020-03193-x
63. Dong J, Li L, Fang X, et al. Exosome-Encapsulated microRNA-127-3p Released from Bone Marrow-Derived Mesenchymal Stem Cells Alleviates Osteoarthritis Through Regulating CDH11-Mediated Wnt/β-Catenin Pathway. *J Pain Res*. 2021;14:297–310. doi:10.2147/JPR.S291472
64. Tao Y, Zhou J, Wang Z, et al. Human bone mesenchymal stem cells-derived exosomal miRNA-361-5p alleviates osteoarthritis by down-regulating DDX20 and inactivating the NF-κB signaling pathway. *Bioorg Chem*. 2021;113:104978. doi:10.1016/j.bioorg.2021.104978
65. Xu H, Xu B, Yokota S-I. BMSC-Derived Exosomes Ameliorate Osteoarthritis by Inhibiting Pyroptosis of Cartilage via Delivering miR-326 Targeting HDAC3 and STAT1//NF- κ B p65 to Chondrocytes. *Mediators Inflamm*. 2021;2021(1):9972805. doi:10.1155/2021/9972805
66. El-Din SS, Aboulhoda BE, Hassouna A, et al. The Role of Intra-Articular Delivery of BM-MSCs-Derived Exosomes in Improving Osteoarthritis: implication of circYAP1/miRNA-21/TLR7 Axis. *Discov Med*. 2024;36(186):1420–1429. doi:10.24976/Discov.Med.202436186.132
67. Mao G, Xu Y, Long D, et al. Exosome-transported circRNA_0001236 enhances chondrogenesis and suppress cartilage degradation via the miR-3677-3p/Sox9 axis. *Stem Cell Res Ther*. 2021;12(1):389. doi:10.1186/s13287-021-02431-5
68. Jin Y, Xu M, Zhu H, et al. Therapeutic effects of bone marrow mesenchymal stem cells-derived exosomes on osteoarthritis. *J Cell Mol Med*. 2021;25(19):9281–9294. doi:10.1111/jcmm.16860

69. Wang Y, Hu K, Liao C, et al. Exosomes-Shuttled lncRNA SNHG7 by Bone Marrow Mesenchymal Stem Cells Alleviates Osteoarthritis Through Targeting miR-485-5p/FSP1 Axis-Mediated Chondrocytes Ferroptosis and Inflammation. *Tissue Eng Regen Med*. 2024;21(8):1203–1216. doi:10.1007/s13770-024-00668-8
70. Wang X, Li Z, Cui Y, et al. Exosomes Isolated From Bone Marrow Mesenchymal Stem Cells Exert a Protective Effect on Osteoarthritis via lncRNA LYRM4-AS1-GRPR-miR-6515-5p. *Front Cell Dev Biol*. 2021;9:644380. doi:10.3389/fcell.2021.644380
71. Wang R, Xu B. TGFβ1-modified MSC-derived exosome attenuates osteoarthritis by inhibiting PDGF-BB secretion and H-type vessel activity in the subchondral bone. *Acta Histochem*. 2022;124(7):151933. doi:10.1016/j.acthis.2022.151933
72. Hu J, Shi ZS, Liu XZ, et al. Exosomes Derived from Runx2-Overexpressing BMSCs Enhance Cartilage Tissue Regeneration and Prevent Osteoarthritis of the Knee in a Rabbit Model. *Stem Cells Int*. 2022;2022:6865041. doi:10.1155/2022/6865041
73. Li J, Ding Z, Li Y, et al. BMSCs-Derived Exosomes Ameliorate Pain Via Abrogation of Aberrant Nerve Invasion in Subchondral Bone in Lumbar Facet Joint Osteoarthritis. *J Orthop Res*. 2020;38(3):670–679. doi:10.1002/jor.24497
74. He L, He T, Xing J, et al. Bone marrow mesenchymal stem cell-derived exosomes protect cartilage damage and relieve knee osteoarthritis pain in a rat model of osteoarthritis. *Stem Cell Res Ther*. 2020;11(1):276. doi:10.1186/s13287-020-01781-w
75. Zhang J, Rong Y, Luo C, et al. Bone marrow mesenchymal stem cell-derived exosomes prevent osteoarthritis by regulating synovial macrophage polarization. *Aging (Albany NY)*. 2020;12(24):25138–25152. doi:10.18632/aging.104110
76. Tang S, Tang T, Gao G, et al. Bone marrow mesenchymal stem cell-derived exosomes inhibit chondrocyte apoptosis and the expression of MMPs by regulating Drp1-mediated mitophagy. *Acta Histochem*. 2021;123(8):151796. doi:10.1016/j.acthis.2021.151796
77. Cheng S, Xu X, Wang R, et al. Chondroprotective effects of bone marrow mesenchymal stem cell-derived exosomes in osteoarthritis. *J Bioenerg Biomembr*. 2024;56(1):31–44. doi:10.1007/s10863-023-09991-6
78. Zhou L, Ye H, Liu L, et al. Human Bone Mesenchymal Stem Cell-Derived Exosomes Inhibit IL-1β-Induced Inflammation in Osteoarthritis Chondrocytes. *Cell J*. 2021;23(4):485–494. doi:10.22074/cellj.2021.7127
79. Li P, Lv S, Jiang W, et al. Exosomes derived from umbilical cord mesenchymal stem cells protect cartilage and regulate the polarization of macrophages in osteoarthritis. *Ann Transl Med*. 2022;10(18):976. doi:10.21037/atm-22-3912
80. Li X, Wang Y, Cai Z, et al. Exosomes from human umbilical cord mesenchymal stem cells inhibit ROS production and cell apoptosis in human articular chondrocytes via the miR-100-5p/NOX4 axis. *Cell Biol Int*. 2021;45(10):2096–2106. doi:10.1002/cbin.11657
81. Wang S, Jiang W, Lv S, et al. Human umbilical cord mesenchymal stem cells-derived exosomes exert anti-inflammatory effects on osteoarthritis chondrocytes. *Aging (Albany NY)*. 2023;15(18):9544–9560. doi:10.18632/aging.205034
82. Klyucherev TO, Peshkova MA, Revokatova DP, et al. The Therapeutic Potential of Exosomes vs. Matrix-Bound Nanovesicles from Human Umbilical Cord Mesenchymal Stromal Cells in Osteoarthritis Treatment. *Int J Mol Sci*. 2024;25(21):11564. doi:10.3390/ijms252111564
83. Yang H, Zhou Y, Ying B, et al. Effects of human umbilical cord mesenchymal stem cell-derived exosomes in the rat osteoarthritis models. *Stem Cells Transl Med*. 2024;13(8):803–811. doi:10.1093/stcltm/szae031
84. Jiang S, Tian G, Yang Z, et al. Enhancement of acellular cartilage matrix scaffold by Wharton's jelly mesenchymal stem cell-derived exosomes to promote osteochondral regeneration. *Bioact Mater*. 2021;6(9):2711–2728. doi:10.1016/j.bioactmat.2021.01.031
85. Wang Z, Yan K, Ge G, et al. Exosomes derived from miR-155-5p-overexpressing synovial mesenchymal stem cells prevent osteoarthritis via enhancing proliferation and migration, attenuating apoptosis, and modulating extracellular matrix secretion in chondrocytes. *Cell Biol Toxicol*. 2021;37(1):85–96. doi:10.1007/s10565-020-09559-9
86. Qiu M, Xie Y, Tan G, et al. Synovial mesenchymal stem cell-derived exosomal miR-485-3p relieves cartilage damage in osteoarthritis by targeting the NRP1-mediated PI3K/Akt pathway: exosomal miR-485-3p relieves cartilage damage. *Heliyon*. 2024;10(2):e24042. doi:10.1016/j.heliyon.2024.e24042
87. Kong R, Zhang J, Ji L, et al. Synovial mesenchymal stem cell-derived exosomal microRNA-320c facilitates cartilage damage repair by targeting ADAM19-dependent Wnt signalling in osteoarthritis rats. *Inflammopharmacology*. 2023;31(2):915–926. doi:10.1007/s10787-023-01142-y
88. Kong R, Gao J, Zhang J, et al. Synovial mesenchymal stem cell-derived exosomal miR-320c enhances chondrogenesis by targeting ADAM19. *Future Med Chem*. 2022;14(2):81–96. doi:10.4155/fmc-2021-0177
89. Qiu M, Liu D, Fu Q. MiR-129-5p shuttled by human synovial mesenchymal stem cell-derived exosomes relieves IL-1β induced osteoarthritis via targeting HMGB1. *Life Sci*. 2021;269:118987. doi:10.1016/j.lfs.2020.118987
90. Zheng T, Li Y, Zhang X, et al. Exosomes Derived From miR-212-5p Overexpressed Human Synovial Mesenchymal Stem Cells Suppress Chondrocyte Degeneration and Inflammation by Targeting ELF3. *Front Bioeng Biotechnol*. 2022;10:816209. doi:10.3389/fbioe.2022.816209
91. Sun W, Qu S, Ji M, et al. BMP-7 modified exosomes derived from synovial mesenchymal stem cells attenuate osteoarthritis by M2 polarization of macrophages. *Heliyon*. 2023;9(9):e19934. doi:10.1016/j.heliyon.2023.e19934
92. Wang Y, Yu D, Liu Z, et al. Exosomes from embryonic mesenchymal stem cells alleviate osteoarthritis through balancing synthesis and degradation of cartilage extracellular matrix. *Stem Cell Res Ther*. 2017;8(1):189. doi:10.1186/s13287-017-0632-0
93. Li Y, Duan J, Lin W, et al. Exosomal miR-93-5p regulated the progression of osteoarthritis by targeting ADAMTS9. *Open Med (Wars)*. 2023;18(1):20230668. doi:10.1515/med-2023-0668
94. Li C, Li W, Pu G, et al. Exosomes derived from miR-338-3p-modified adipose stem cells inhibited inflammation injury of chondrocytes via targeting RUNX2 in osteoarthritis. *J Orthop Surg Res*. 2022;17(1):567. doi:10.1186/s13018-022-03437-2
95. Wang Y, Fan A, Lu L, et al. Exosome modification to better alleviates endoplasmic reticulum stress induced chondrocyte apoptosis and osteoarthritis. *Biochem Pharmacol*. 2022;206:115343. doi:10.1016/j.bcp.2022.115343
96. Li F, Xu Z, Xie Z, et al. Adipose mesenchymal stem cells-derived exosomes alleviate osteoarthritis by transporting microRNA −376c-3p and targeting the WNT-beta-catenin signaling axis. *Apoptosis*. 2023;28(3–4):362–378. doi:10.1007/s10495-022-01787-0
97. Meng C, Na Y, Han C, et al. Exosomal miR-429 derived from adipose-derived stem cells ameliorated chondral injury in osteoarthritis via autophagy by targeting FEZ2. *Int Immunopharmacol*. 2023;120:110315. doi:10.1016/j.intimp.2023.110315
98. Zhao C, Chen JY, Peng WM, et al. Exosomes from adipose-derived stem cells promote chondrogenesis and suppress inflammation by upregulating miR-145 and miR-221. *Mol Med Rep*. 2020;21(4):1881–1889. doi:10.3892/mmr.2020.10982
99. Liu Y, Zeng Y, Si HB, et al. Exosomes Derived From Human Urine-Derived Stem Cells Overexpressing miR-140-5p Alleviate Knee Osteoarthritis Through Downregulation of VEGFA in a Rat Model. *Am J Sports Med*. 2022;50(4):1088–1105. doi:10.1177/03635465221073991

100. Zhou JP, Peng SS, Xu J, et al. Exploring the therapeutic potential of urine-derived stem cell exosomes in temporomandibular joint osteoarthritis. *FASEB j*. 2024;38(15):e23852. doi:10.1096/fj.202400448RR
101. Lin T, Wu N, Wang L, et al. Inhibition of chondrocyte apoptosis in a rat model of osteoarthritis by exosomes derived from miR-140-5p-overexpressing human dental pulp stem cells. *Int J Mol Med*. 2021;47(3):7. doi:10.3892/ijmm.2020.4840
102. Fu Y, Cui S, Zhou Y, et al. Dental Pulp Stem Cell-Derived Exosomes Alleviate Mice Knee Osteoarthritis by Inhibiting TRPV4-Mediated Osteoclast Activation. *Int J Mol Sci*. 2023;24(5):4926. doi:10.3390/ijms24054926
103. Luo P, Jiang C, Ji P, et al. Exosomes of stem cells from human exfoliated deciduous teeth as an anti-inflammatory agent in temporomandibular joint chondrocytes via miR-100-5p/mTOR. *Stem Cell Res Ther*. 2019;10(1):216. doi:10.1186/s13287-019-1341-7
104. Lin CY, Naruphontjirakul P, Huang TY, et al. The Exosomes of Stem Cells from Human Exfoliated Deciduous Teeth Suppress Inflammation in Osteoarthritis. *Int J Mol Sci*. 2024;25(16):8560. doi:10.3390/ijms25168560
105. Chen J, Tan Y, Chen Z, et al. Exosomes derived from primary cartilage stem/progenitor cells promote the repair of osteoarthritic chondrocytes by modulating immune responses. *Int Immunopharmacol*. 2024;143(Pt 2):113397. doi:10.1016/j.intimp.2024.113397
106. Zhang FX, Dou Y, Zhang B, et al. Skeletal Stem Cell-Derived Exosomes Promote Meniscal Tear Healing and Ameliorate Secondary Osteoarthritis. *Am J Sports Med*. 2024;52(10):2512–2523. doi:10.1177/03635465241262002
107. Wu S, Luo J, Zhang X, et al. Synovia tissue-specific exosomes participate in the dual variation of the osteoarthritis microenvironment via miR-182. *Exp Cell Res*. 2024;436(2):113981. doi:10.1016/j.yexcr.2024.113981
108. Ji Y, Xiong L, Zhang G, et al. Synovial fluid exosome-derived miR-182-5p alleviates osteoarthritis by downregulating TNFAIP8 and promoting autophagy through LC3 signaling. *Int Immunopharmacol*. 2023;125(Pt A):111177. doi:10.1016/j.intimp.2023.111177
109. Wang H, Zhang Y, Zhang C, et al. Exosomes derived from miR-146a-overexpressing fibroblast-like synoviocytes in cartilage degradation and macrophage M1 polarization: a novel protective agent for osteoarthritis? *Front Immunol*. 2024;15:1361606. doi:10.3389/fimmu.2024.1361606
110. Zhou Y, Ming J, Li Y, et al. Exosomes derived from miR-126-3p-overexpressing synovial fibroblasts suppress chondrocyte inflammation and cartilage degradation in a rat model of osteoarthritis. *Cell Death Discov*. 2021;7(1):37. doi:10.1038/s41420-021-00418-y
111. Lai C, Liao B, Peng S, et al. Synovial fibroblast-miR-214-3p-derived exosomes inhibit inflammation and degeneration of cartilage tissues of osteoarthritis rats. *Mol Cell Biochem*. 2023;478(3):637–649. doi:10.1007/s11010-022-04535-9
112. Kong R, Ji L, Pang Y, et al. Exosomes from osteoarthritic fibroblast-like synoviocytes promote cartilage ferroptosis and damage via delivering microRNA-19b-3p to target SLC7A11 in osteoarthritis. *Front Immunol*. 2023;14:1181156. doi:10.3389/fimmu.2023.1181156
113. Da-Wa ZX, Jun M, Chao-Zheng L, et al. Exosomes Derived from M2 Macrophages Exert a Therapeutic Effect via Inhibition of the PI3K/AKT/mTOR Pathway in Rats with Knee Osteoarthritic. *Biomed Res Int*. 2021;2021(1):7218067. doi:10.1155/2021/7218067
114. Si W, Wei H, Chen W, et al. Exosomal microRNA-363 mediates the destructive effect of M1 macrophages on chondrocytes by repressing G3BP2. *Exp Cell Res*. 2024;442(2):114276. doi:10.1016/j.yexcr.2024.114276
115. Yang RZ, Zheng HL, Xu WN, et al. Vascular endothelial cell-secreted exosomes facilitate osteoarthritis pathogenesis by promoting chondrocyte apoptosis. *Aging (Albany NY)*. 2021;13(3):4647–4662. doi:10.18632/aging.202506
116. Mao G, Hu S, Zhang Z, et al. Exosomal miR-95-5p regulates chondrogenesis and cartilage degradation via histone deacetylase 2/8. *J Cell Mol Med*. 2018;22(11):5354–5366. doi:10.1111/jcmm.13808
117. Zheng L, Wang Y, Qiu P, et al. Primary chondrocyte exosomes mediate osteoarthritis progression by regulating mitochondrion and immune reactivity. *Nanomedicine (Lond)*. 2019;14(24):3193–3212. doi:10.2217/nnm-2018-0498
118. Liu Q, Wang R, Hou S, et al. Chondrocyte-derived exosomes promote cartilage calcification in temporomandibular joint osteoarthritis. *Arthritis Res Ther*. 2022;24(1):44. doi:10.1186/s13075-022-02738-5
119. Xu W, Zhang Y, Li L, et al. Osteocyte-derived exosomes regulate the DLX2/wnt pathway to alleviate osteoarthritis by mediating cartilage repair. *Autoimmunity*. 2024;57(1):2364686. doi:10.1080/08916934.2024.2364686
120. Liu J, Wu X, Lu J, et al. Exosomal transfer of osteoclast-derived miRNAs to chondrocytes contributes to osteoarthritis progression. *Nat Aging*. 2021;1(4):368–384. doi:10.1038/s43587-021-00050-6
121. Dai J, Hu Z, Zeng F, et al. Osteoclast-derived exosomal miR-212-3p suppressed the anabolism and accelerated the catabolism of chondrocytes in osteoarthritis by targeting TGF-β1/Smad2 signaling. *Arch Biochem Biophys*. 2024;751:109827. doi:10.1016/j.abb.2023.109827
122. Huang C, Zhao Y, Lin S, et al. Characterization of human placenta-derived exosome (pExo) as a potential osteoarthritis disease modifying therapeutic. *Arthritis Res Ther*. 2023;25(1):229. doi:10.1186/s13075-023-03219-z
123. Xu C, Mi Z, Dong Z, et al. Platelet-Derived Exosomes Alleviate Knee Osteoarthritis by Attenuating Cartilage Degeneration and Subchondral Bone Loss. *Am J Sports Med*. 2023;51(11):2975–2985. doi:10.1177/03635465231188122
124. Liu X, Wang L, Ma C, et al. Exosomes derived from platelet-rich plasma present a novel potential in alleviating knee osteoarthritis by promoting proliferation and inhibiting apoptosis of chondrocyte via Wnt/β-catenin signaling pathway. *J Orthop Surg Res*. 2019;14(1):470. doi:10.1186/s13018-019-1529-7
125. Chang L, Kan L. Mesenchymal Stem Cell-Originated Exosomal Circular RNA circFBXW7 Attenuates Cell Proliferation, Migration and Inflammation of Fibroblast-Like Synoviocytes by Targeting miR-216a-3p/HDAC4 in Rheumatoid Arthritis. *J Inflamm Res*. 2021;14:6157–6171. doi:10.2147/JIR.S336099
126. Su Y, Liu Y, Ma C, et al. Mesenchymal stem cell-originated exosomal lncRNA HAND2-AS1 impairs rheumatoid arthritis fibroblast-like synoviocyte activation through miR-143-3p/TNFAIP3/NF-κB pathway. *J Orthop Surg Res*. 2021;16(1):116. doi:10.1186/s13018-021-02248-1
127. Ma W, Tang F, Xiao L, et al. miR-205-5p in exosomes divided from chondrogenic mesenchymal stem cells alleviated rheumatoid arthritis via regulating MDM2 in fibroblast-like synoviocytes. *J Musculoskelet Neuronal Interact*. 2022;22(1):132–141.
128. Wu L, Wang Z, Hou Z, et al. Exosomal MicroRNA-23-5p Derived from Bone Marrow Mesenchymal Stem Cells Relieves Inflammatory Response in Rheumatoid Arthritis. *Journal of Biomaterials and Tissue Engineering*. 2022;12(5):939–946. doi:10.1166/jbt.2022.2997
129. Huang Y, Lu D, Ma W, et al. miR-223 in exosomes from bone marrow mesenchymal stem cells ameliorates rheumatoid arthritis via downregulation of NLRP3 expression in macrophages. *Mol Immunol*. 2022;143:68–76. doi:10.1016/j.molimm.2022.01.002
130. Ye H, Wu X, Shen Y, et al. Exosomal lncRNA TUG1 derived from BMSC ameliorate collagen-induced arthritis via BLIMP1-mediated Th17/Treg balance. *Int Immunopharmacol*. 2024;142(Pt A):113072. doi:10.1016/j.intimp.2024.113072
131. Wang L, Li F, Wang L, et al. Exosomes Derived from Bone Marrow Mesenchymal Stem Cells Alleviate Rheumatoid Arthritis Symptoms via Shuttling Proteins. *J Proteome Res*. 2024;23(4):1298–1312. doi:10.1021/acs.jproteome.3c00697

132. Xu W, Liu X, Qu W, et al. Exosomes derived from fibrinogen-like protein 1-overexpressing bone marrow-derived mesenchymal stem cells ameliorates rheumatoid arthritis. *Bioengineered*. 2022;13(6):14545–14561. doi:10.1080/21655979.2022.2090379
133. Wang X, Shi T, Jiao Y, et al. Human umbilical mesenchymal stem cell-derived exosomes alleviate bone destruction and regulate bone immunity via the aryl hydrocarbon receptor to treat rheumatoid arthritis. *Int Immunopharmacol*. 2024;143(Pt 2):113340. doi:10.1016/j.intimp.2024.113340
134. Huang Y, Chen L, Chen D, et al. Exosomal microRNA-140-3p from human umbilical cord mesenchymal stem cells attenuates joint injury of rats with rheumatoid arthritis by silencing SGK1. *Mol Med*. 2022;28(1):36. doi:10.1186/s10020-022-00451-2
135. Mi L, Gao J, Li N, et al. Human umbilical cord mesenchymal stem cell-derived exosomes loaded miR-451a targets ATF2 to improve rheumatoid arthritis. *Int Immunopharmacol*. 2024;127:111365. doi:10.1016/j.intimp.2023.111365
136. Fu Y, Li J, Zhang Z, et al. Umbilical cord mesenchymal stem cell-derived exosomes alleviate collagen-induced arthritis by balancing the population of Th17 and regulatory T cells. *FEBS Lett*. 2022;596(20):2668–2677. doi:10.1002/1873-3468.14460
137. Zhang J, Zhang Y, Ma Y, et al. Therapeutic Potential of Exosomal circRNA Derived from Synovial Mesenchymal Cells via Targeting circEDIL3/miR-485-3p/PIAS3/STAT3/VEGF Functional Module in Rheumatoid Arthritis. *Int J Nanomedicine*. 2021;16:7977–7994. doi:10.2147/IJN.S333465
138. Tian X, Wei W, Cao Y, et al. Gingival mesenchymal stem cell-derived exosomes are immunosuppressive in preventing collagen-induced arthritis. *J Cell Mol Med*. 2022;26(3):693–708. doi:10.1111/jcmm.17086
139. Chen J, Liu M, Luo X, et al. Exosomal miRNA-486-5p derived from rheumatoid arthritis fibroblast-like synoviocytes induces osteoblast differentiation through the Tob1/BMP/Smad pathway. *Biomater Sci*. 2020;8(12):3430–3442. doi:10.1039/C9BM01761E
140. Liu D, Fang Y, Rao Y, et al. Synovial fibroblast-derived exosomal microRNA-106b suppresses chondrocyte proliferation and migration in rheumatoid arthritis via down-regulation of PDK4. *J Mol Med (Berl)*. 2020;98(3):409–423. doi:10.1007/s00109-020-01882-2
141. Nakamachi Y, Uto K, Hayashi S, et al. Exosomes derived from synovial fibroblasts from patients with rheumatoid arthritis promote macrophage migration that can be suppressed by miR-124-3p. *Heliyon*. 2023;9(4):e14986. doi:10.1016/j.heliyon.2023.e14986
142. Li G, Fang Y, Xu N, et al. Fibroblast-like synoviocytes-derived exosomal circFTO deteriorates rheumatoid arthritis by enhancing N6-methyladenosine modification of SOX9 in chondrocytes. *Arthritis Res Ther*. 2024;26(1):56. doi:10.1186/s13075-024-03290-0
143. Yao X, Wang Q, Zeng P, et al. LncRNA HOTTIP from synovial fibroblast-derived exosomes: a novel molecular target for rheumatoid arthritis through the miR-1908-5p/STAT3 axis. *Exp Cell Res*. 2021;409(2):112943. doi:10.1016/j.yexcr.2021.112943
144. Chen M, Li MH, Zhang N, et al. Pro-angiogenic effect of exosomal microRNA-103a in mice with rheumatoid arthritis via the downregulation of hepatocyte nuclear factor 4 alpha and activation of the JAK/STAT3 signaling pathway. *J Biol Regul Homeost Agents*. 2021;35(2):629–640. doi:10.23812/20-537-A
145. Rao Y, Fang Y, Tan W, et al. Delivery of Long Non-coding RNA NEAT1 by Peripheral Blood Monouclear Cells-Derived Exosomes Promotes the Occurrence of Rheumatoid Arthritis via the MicroRNA-23a/MDM2/SIRT6 Axis. *Front Cell Dev Biol*. 2020;8:551681. doi:10.3389/fcell.2020.551681
146. György B, Szabó TG, Pásztói M, et al. Membrane vesicles, current state-of-the-art: emerging role of extracellular vesicles. *Cell Mol Life Sci*. 2011;68(16):2667–2688. doi:10.1007/s00018-011-0689-3
147. Zhuang X, Grizzle W et al. Treatment of brain inflammatory diseases by delivering exosome encapsulated anti-inflammatory drugs from the nasal region to the brain. *Mol Ther*. 2011;19(10):1769–1779. doi: 10.1038/mt.2011.164
148. Michael A, Bajracharya SD, Yuen PS et al. Exosomes from human saliva as a source of microRNA biomarkers. *Oral Dis*. 2010;16(1):34–38. doi: 10.1111/j.1601-0825.2009.01604.x
149. Thierry AR, El Messaoudi S, Gahan PB et al. Origins, structures, and functions of circulating DNA in oncology. *Cancer Metastasis Rev*. 2016;35(3):347–376. doi: 10.1007/s10555-016-9629-x
150. Trujillo CM, Long TM. Document co-citation analysis to enhance transdisciplinary research. *Sci Adv*. 2018;4(1):e1701130. doi:10.1126/sciadv.1701130
151. Denzer K, Kleijmeer MJ, Heijnen HF, et al. Exosome: from internal vesicle of the multivesicular body to intercellular signaling device. *J Cell Sci*. 2000;113(19):3365–3374. doi:10.1242/jcs.113.19.3365
152. Valadi H, Ekström K, Bossios A, et al. Exosome-mediated transfer of mRNAs and microRNAs is a novel mechanism of genetic exchange between cells. *Nat Cell Biol*. 2007;9(6):654–659. doi:10.1038/ncb1596
153. Rachul C, Marcon AR, Collins B, et al. COVID-19 and 'immune boosting' on the internet: a content analysis of Google search results. *BMJ Open*. 2020;10(10):e040989. doi:10.1136/bmjopen-2020-040989
154. Wang F, Ma Y, Xu S, et al. Prevalence and risk of COVID-19 in patients with rheumatic diseases: a systematic review and meta-analysis. *Clin Rheumatol*. 2022;41(7):2213–2223. doi:10.1007/s10067-022-06087-1
155. EL Andaloussi S, Mäger I, Breakefield XO, et al. Extracellular vesicles: biology and emerging therapeutic opportunities. *Nat Rev Drug Discov*. 2013;12(5):347–357. doi:10.1038/nrd3978
156. Théry C, Ostrowski M, Segura E. Membrane vesicles as conveyors of immune responses. *Nat Rev Immunol*. 2009;9(8):581–593. doi:10.1038/nri2567
157. Théry C, Zitvogel L, Amigorena S. Exosomes: composition, biogenesis and function. *Nat Rev Immunol*. 2002;2(8):569–579. doi:10.1038/nri855
158. Wang C, Silverman RM, Shen J, et al. Distinct metabolic programs induced by TGF-β1 and BMP2 in human articular chondrocytes with osteoarthritis. *J Orthop Translat*. 2018;12:66–73. doi:10.1016/j.jot.2017.12.004
159. Liu B, Xian Y, Chen X, et al. Inflammatory Fibroblast-Like Synoviocyte-Derived Exosomes Aggravate Osteoarthritis via Enhancing Macrophage Glycolysis. *Adv Sci (Weinh)*. 2024;11(14):e2307338. doi:10.1002/advs.202307338
160. Domenis R, Zanutel R, Caponnetto F, et al. Characterization of the Proinflammatory Profile of Synovial Fluid-Derived Exosomes of Patients with Osteoarthritis. *Mediators Inflamm*. 2017;2017:4814987. doi:10.1155/2017/4814987
161. Yu F, Xie C, Sun J, et al. Circular RNA expression profiles in synovial fluid: a promising new class of diagnostic biomarkers for osteoarthritis. *Int J Clin Exp Pathol*. 2018;11(3):1338–1346.
162. Li Z, Wang Y, Xiao K, et al. Emerging Role of Exosomes in the Joint Diseases. *Cell Physiol Biochem*. 2018;47(5):2008–2017. doi:10.1159/000491469

163. Withrow J, Murphy C, Liu Y, et al. Extracellular vesicles in the pathogenesis of rheumatoid arthritis and osteoarthritis. *Arthritis Res Ther*. 2016;18(1):286. doi:10.1186/s13075-016-1178-8
164. Maeda Y, Farina NH, Matzelle MM, et al. Synovium-Derived MicroRNAs Regulate Bone Pathways in Rheumatoid Arthritis. *J Bone Miner Res*. 2017;32(3):461–472. doi:10.1002/jbmr.3005
165. Chen R, Zhou D, Chen Y, et al. Understanding the role of exosomal lncRNAs in rheumatic diseases: a review. *PeerJ*. 2023;11:e16434. doi:10.7717/peerj.16434
166. Fang F, Hua MQ, Yu GM. Study of the mechanism of fibroblast-like synoviocytes-derived exosomes inducing macrophages M1 polarization and $CD8^{+}$T cells immune regulation ferroptosis and autophagy in rheumatoid arthritis. *Immunol Lett*. 2024;270:106936. doi:10.1016/j.imlet.2024.106936
167. Greisen SR, Yan Y, Hansen AS, et al. Extracellular Vesicles Transfer the Receptor Programmed Death-1 in Rheumatoid Arthritis. *Front Immunol*. 2017;8:851. doi:10.3389/fimmu.2017.00851
168. Wu H, Chen Q, Wang S, et al. Serum exosomes lncRNAs: TCONS_I2_00013502 and ENST00000363624 are new diagnostic markers for rheumatoid arthritis. *Front Immunol*. 2024;15:1419683. doi:10.3389/fimmu.2024.1419683
169. Yu Y, Park S, Lee H, et al. Exosomal hsa-miR-335-5p and hsa-miR-483-5p are novel biomarkers for rheumatoid arthritis: a development and validation study. *Int Immunopharmacol*. 2023;120:110286. doi:10.1016/j.intimp.2023.110286
170. Zhou TS, Yang CL, Wang JQ, et al. Identification of serum exosomal lncRNAs and their potential regulation of characteristic genes of fibroblast-like synoviocytes in rheumatoid arthritis. *Int Immunopharmacol*. 2024;143(Pt2):113382. doi:10.1016/j.intimp.2024.113382
171. Lai P, Weng J, Guo L, et al. Novel insights into MSC-EVs therapy for immune diseases. *Biomark Res*. 2019;7(1):6. doi:10.1186/s40364-019-0156-0
172. Perico L, Morigi M, Rota C, et al. Human mesenchymal stromal cells transplanted into mice stimulate renal tubular cells and enhance mitochondrial function. *Nat Commun*. 2017;8(1):983. doi:10.1038/s41467-017-00937-2
173. Di Nicola M, Carlo-Stella C, Magni M, et al. Human bone marrow stromal cells suppress T-lymphocyte proliferation induced by cellular or nonspecific mitogenic stimuli. *Blood*. 2002;99(10):3838–3843. doi:10.1182/blood.V99.10.3838
174. Duan L, Xu X, Xu L, et al. Exosome-Mediated Drug Delivery for Cell-Free Therapy of Osteoarthritis. *Curr Med Chem*. 2021;28(31):6458–6483. doi:10.2174/0929867327666201118161232
175. Xia Y, Zhang J, Liu G, et al. Immunogenicity of Extracellular Vesicles. *Adv Mater*. 2024;36(33):e2403199. doi:10.1002/adma.202403199
176. Chu CH, Lee RP, Wu WT, et al. Advancing Osteoarthritis Treatment: the Therapeutic Potential of Mesenchymal Stem Cell-Derived Exosomes and Biomaterial Integration. *Biomedicines*. 2024;12(11):2478. doi:10.3390/biomedicines12112478
177. Lin Z, Xu G, Lu X, et al. Chondrocyte-targeted exosome-mediated delivery of Nrf2 alleviates cartilaginous endplate degeneration by modulating mitochondrial fission. *J Nanobiotechnology*. 2024;22(1):281. doi:10.1186/s12951-024-02517-1
178. Jiang X, Shi L, Feng H, et al. Engineered Exosomes Loaded with Triptolide: an Innovative Approach to Enhance Therapeutic Efficacy in Rheumatoid Arthritis. *Int Immunopharmacol*. 2024;129:111677. doi:10.1016/j.intimp.2024.111677
179. Wu X, Tao W, Lan Z, et al. pH-Responsive Engineered Exosomes Enhance Endogenous Hyaluronan Production by Reprogramming Chondrocytes for Cartilage Repair. *Adv Healthc Mater*. 2025;14(10):e2405126. doi:10.1002/adhm.202405126
180. Villani C, Murugan P, George A. Exosome-Laden Hydrogels as Promising Carriers for Oral and Bone Tissue Engineering: insight into Cell-Free Drug Delivery. *Int J Mol Sci*. 2024;25(20):11092. doi:10.3390/ijms252011092
181. Diez-Guardia V, Tian Y, Guo Y, et al. Controlled Release of Human Dental Pulp Stem Cell-Derived Exosomes from Hydrogels Attenuates Temporomandibular Joint Osteoarthritis. *Adv Healthc Mater*. 2024:e2402923. doi:10.1002/adhm.202402923
182. Cao H, Li W, Zhang H, et al. Bio-nanoparticles loaded with synovial-derived exosomes ameliorate osteoarthritis progression by modifying the oxidative microenvironment. *J Nanobiotechnology*. 2024;22(1):271. doi:10.1186/s12951-024-02538-w
183. Yang L, Li W, Zhao Y, et al. Magnetic Polysaccharide Mesenchymal Stem Cells Exosomes Delivery Microcarriers for Synergistic Therapy of Osteoarthritis. *ACS Nano*. 2024;18(31):20101–20110. doi:10.1021/acsnano.4c01406