Journal of Inflammation Research

Dovepress
open access to scientific and medical research

Open Access Full Text Article

REVIEW

Diagnostic and Therapeutic Roles of Extracellular Vesicles and Their Enwrapped ncRNAs in Rheumatoid Arthritis

Ya-ru Liu[1,2,*], Jie-Quan Wang[3–5,*], Ling Fang[1,2], Quan Xia[1,2]

[1]Department of Pharmacy, The First Affiliated Hospital of Anhui Medical University, Hefei, 230022, People's Republic of China; [2]The Grade 3 Pharmaceutical Chemistry Laboratory of State Administration of Traditional Chinese Medicine, Hefei, 230022, People's Republic of China; [3]Department of Pharmacy, Affiliated Psychological Hospital of Anhui Medical University, Hefei, 230000, People's Republic of China; [4]Department of Pharmacy, Hefei Fourth People's Hospital, Hefei, 230000, People's Republic of China; [5]Psychopharmacology Research Laboratory, Anhui Mental Health Center, Hefei, 230000, People's Republic of China

*These authors contributed equally to this work

Correspondence: Ling Fang; Quan Xia, Department of Pharmacy, The First Affiliated Hospital of Anhui Medical University, Hefei, Anhui, 230022, People's Republic of China, Email fangling@ahmu.edu.cn; xiaquan2010@163.com

Abstract: Rheumatoid arthritis (RA) is a systemic inflammatory disease whose precise pathogenesis remains mysterious. The involvement of epigenetic regulation in the pathogenesis of RA is one of the most anticipated findings, among which non-coding RNAs (ncRNAs) hold great application promise as diagnostic and therapeutic biomarkers for RA. Extracellular vesicles (EVs) are a heterogeneous group of nano-sized, membrane-enclosed vesicles that mediate intercellular communication and substance exchange, especially the transfer of ncRNAs from donor cells, thereby regulating the functional activities and biological processes of recipient cells. In light of the significant correlation between EVs, ncRNAs, and RA, we first documented expression levels of EVs and their-encapsulated ncRNAs in RA individuals, and methodically discussed their-implicated signaling pathways and phenotypic changes. The last but not least, we paied special attention to the therapeutic benefits of gene therapy reagents specifically imitating or silencing candidate ncRNAs with exosomes as carriers on RA animal models, and briefly highlighted their clinical application advantage and foreground. In conclusion, the present review may be conducive to a deeper comprehension of the diagnostic and therapeutic roles of EVs-enwrapped ncRNAs in RA, with special emphasis on exosomal ncRNAs, which may offer hints for the monitoring and treatment of RA.

Keywords: rheumatoid arthritis, extracellular vesicles, non-coding RNAs, diagnostic and therapeutic role

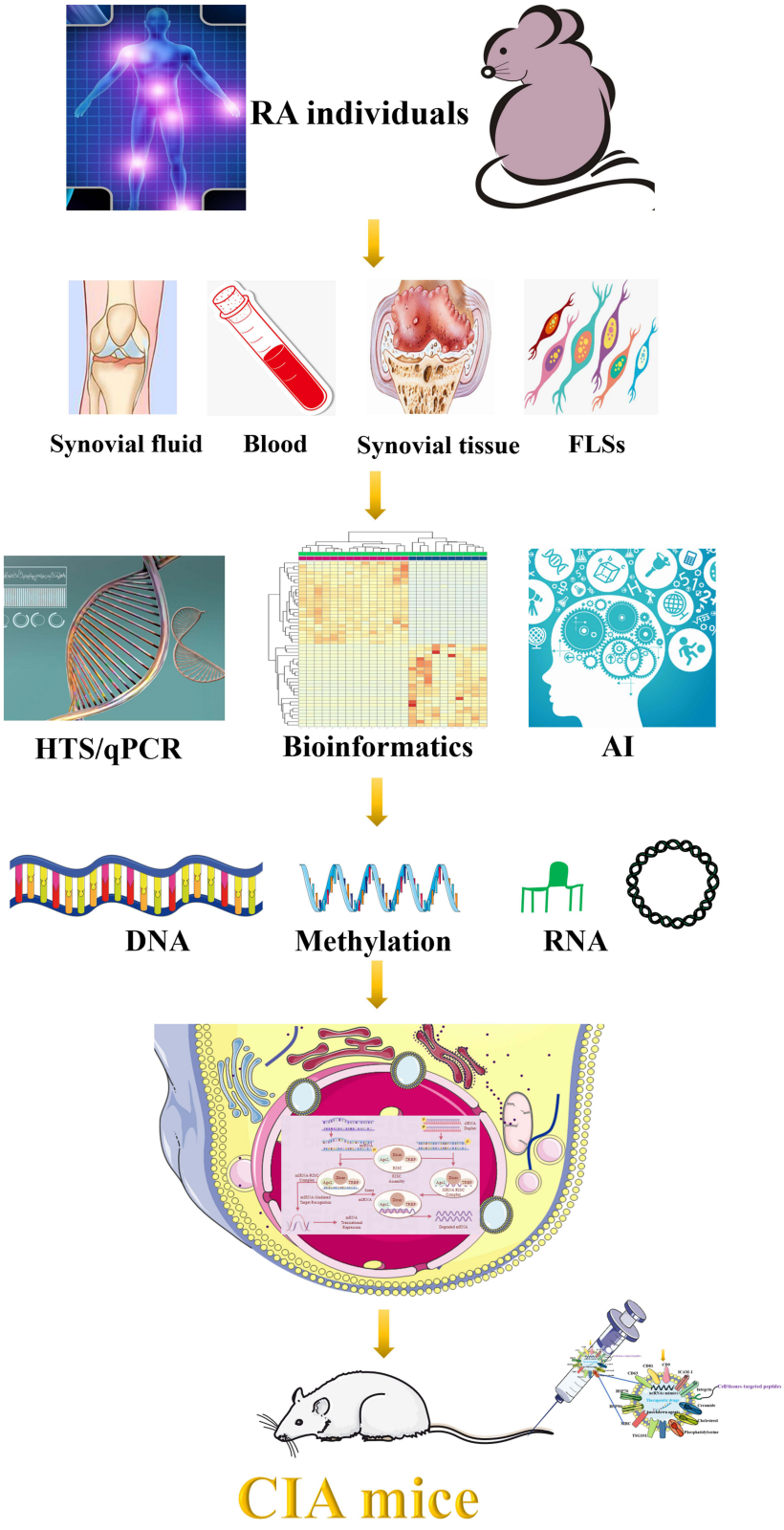
Introduction

Rheumatoid arthritis (RA) is one of the most prevalent autoimmune diseases that mostly impairs joint function.[1] The main pathogenic characteristics of RA are synovial hyperplasia, immune infiltration, and pannus formation.[2] Epidemiological studies have shown that the global incidence of RA falls between 0.5% and 1.0%, with significant geographical, ethnic, and gender differences.[3] Although RA can be clinically diagnosed by detecting antibodies against cyclic citrullinated peptides (ACPA) and rheumatoid factors (RF),[4] diagnosis, prediction and prognosis of RA remains challenging in the absence of available laboratory biomarkers. The widely used disease-modifying anti-rheumatic drugs (DMARDs), such as conventional synthetic DMARDs, biological DMARDs and targeted synthetic DMARDs can improve the outlook or delay RA progression, but cannot drastically cure RA.[5] An enhanced knowledge of cellular and molecular mechanisms that derive RA may shed light on its prediction, risk assessment, prognosis and treatment.

RA may be attributed to a complex interplay between susceptibility genes, immunologic derangement, environmental factor, and epigenetic regulation.[6] As research progresses, noncoding RNAs (ncRNAs), together with histone modification, DNA methylation, and chromatin remodeling, generate heritable phenotypic changes, thus engaging in the genesis

Received: 11 April 2024
Accepted: 2 August 2024
Published: 16 August 2024

Graphical Abstract



and progression of RA.[7] Extracellular vesicles (EVs) can deliver bioactive components such as ncRNAs, messenger RNAs, proteins, and lipids into nearby or distant cells that mediate intercellular communication.[8] A number of studies have found a strong correlation between EVs, ncRNAs, and RA, indicating the possible involvement of dysregulated EVs and EVs-derived ncRNAs in RA-related signaling pathways and biological processes.[9,10]

Several exosomal ncRNAs exhibited excellent sensitivity and specificity in the prediction and diagnosis of RA, and may serve as non-invasive biomarkers for RA.[11,12] An increasing number of circulating ncRNAs such as miR-132-3p, miR-146a-5p, miR-125b, and miR-155-5p have been proven to connect with therapeutic efficacy of DMARDs.[13,14] Highly enriched and stable exosomal ncRNAs may be available for indicating therapeutic responses and the severity of RA symptoms. Therapeutic reagents shuttled by exosomes may not only achieve tissue targeting and increase the stability, but also elevate treatment efficacy and partially cure RA by mimicking or silencing candidate ncRNAs, which displayed favorable application benefits and prospects in the management of RA.[15,16]

A greater comprehension of functional roles and regulatory mechanisms of EVs-wrapped ncRNAs in RA will enable the exploitation of available diagnostic and therapeutic biomarkers. Herein, we surveyed the dysregulated expression of EVs, focusing particularly on exosomes and their-encapsulated ncRNAs in RA individuals, and then discussed relevant biological processes and phenotypic alterations in the course of RA. Finally, we systematically reviewed the therapeutic effects of exosomes-shuttled ncRNAs mimics or knock-down reagents on RA. In summary, this review will provide a theoretical basis and practical reference for the development of trustworthy laboratory biomarkers, therapeutic targets, and target-based biotechnological drugs for RA.

Overview of EVs

As early as 1967, platelets were found to release microparticles (MPs) with agglutinating activity.[17] In 1981, Trams et al observed a set of vesicle-like structures with a diameter of 40–1000 nm.[18] Pan and Johnstone isolated EVs from cultured reticulocytes of sheep.[19] Since then, many unexpected roles of EVs were coming to light. Prostatic or epididymis-derived EVs allowed the transfer of proteins to sperm membrane, aiding in sperm maturation.[20] Another study indicated the importance of EVs biogenesis for the quality control of membrane proteins, such as selective endocytosis of the transferrin receptor and germination of "Juno" from the zygote surface after fertilization.[21] A significant node was that vesicles were officially named "exosomes" in 1987. B lymphocytes and dendritic cells secreted exosomes with antigen-presenting properties, carrying MHC-II, adhesion factors, and costimulatory factors, which can activate antitumor response of CD4 and CTL cells.[22,23] Valadi et al uncovered exosomes-mediated intercellular exchange of genetic material and epigenetic characteristics.[24] Exosomes can be secreted and internalized by diverse kinds of cells, supporting the universality of exosomes-delivery in human health and disease.[25]

EVs are membrane-bound vesicles with a phospholipid bilayer structure that widely exist in a range of body fluids.[26] Ectosomes consisting of microvesicles, apoptotic bodies and MPs are generated by outbidding and shedding from the cytoplasmic membrane.[27] Exosomes ranging in diameter from 40 to 160 nm are produced by the invagination of multivesicular body (MVBs) membranes containing intraluminal vesicles (ILVs) and subsequent fusion with the cytoplasmic membrane, typically expressing CD63, CD81, and CD9.[28] The membrane prevented the degradation of internal RNAs, and exosomal ncRNAs can reflect parental cell status and serve as valuable biomarkers.[8] Given that exosomes cannot self-replicate and avoid immune rejection, vascular occlusion, and mutations,[29] there are no ethical restriction. Owing to high stability and small size, exosomes may cross physiological barriers and improve the efficiency of action.[30] Engineered exosomes like RVG-Lamp2b have good biocompatibility, stability, immunogenicity and low toxicity, and can be applied as therapeutic carriers for brain diseases.[31,32] When gene therapy reagents are loaded onto exosomes from donors, such as mesenchymal stem cells (MSCs), they may have a dual therapeutic effect on genetic diseases.[33]

Potential Roles of EVs in the Pathogenesis of RA

Leukocytes and platelets-derived MPs in synovial fluid and plasma were more abundant in RA patients than in osteoarthritis (OA) patients and healthy controls (HCs), indicating EVs-mediated dynamic crosstalk between circulation and joint.[34] Another study showed the abundance of exosomes in synovial fluid of RA patients was higher than that of

patients with OA, gout, and ankylosing spondylitis, hinting at a RA-specific "synovial signature of osteoclastogenesis" of synovial fluid-derived exosomes.[35] A meta-analysis concluded that EVs, particularly from platelets and immune cells, appeared to be increased in synovial fluid and plasma of RA patients, which may enhance inflammatory signals.[36] Distler et al found that activated or apoptotic immune cells-derived MPs were evidently augmented and enriched in synovial fluid of RA patients, which may be a trigger for bone erosion.[37] Conversely, Headland et al found that the concentration of neutrophil-derived MVs in synovial fluid of RA patients was relatively elevated compared with paired plasma, which seemed to be a responding mechanism to delay arthritis progression.[38] An observational study suggested the presence of dysregulated plasma-derived exosomal protein profiles in RA patients.[39]

EVs-mediated pathogenic processes such as intestinal flora alteration, immune complex formation, antigen presentation, chondrocytes apoptosis, fibroblast-like synoviocytes (FLSs) proliferation, inflammatory cascade reaction, and extracellular matrix (ECM) degradation were involved in the pathogenesis of RA. Circulating EVs from seropositive RA patients can activate monocytes and stimulate the release of pro-inflammatory factors.[40] Circulating immune complex EVs from RA patients can induce the production of M1 macrophages, enhance T-cell proliferation, and decrease the frequency of B cells death.[41] RA synovial fibroblasts (RASFs)-derived EVs suppressed the proliferation, mineralization and differentiation of chondrocytes and osteoblasts, and may play a catalytic role in cartilage failure.[42] Synovial fluid-derived EVs from RA patients were more easily detected and had greater osteoclastogenic potential than those of patients with ankylosing spondylitis and OA.[43] EVs from synovial fluid and plasma of RA patients transported cellular contents acting as TLR ligands, which then invaded synovial tissues and triggered inflammatory responses.[44,45] Plasma-derived EVs from RA patients activated NF-κB pathway in HEK 293T cells expressing TLR4 and MD-2 receptor, suggesting that EVs may sense oxidative stress to promote RA progression by modulating ligand-binding TLR4.[46] The increase of EVs released by RASFs after ferroptosis may be compensatory mechanism of cell damage repair secondary, but cannot thoroughly prevent RA deterioration.[47] EVs isolated from tissues exhibited good specificity and accuracy in reflecting the microenvironment, which may contribute to the study of EVs-associated synovial microenvironment in RA.[48] (Figure 1)

Therapeutic Potential of EVs on RA

MSCs are a subset of pluripotent stem cells that possess multi-differentiated, regenerative, and immunomodulatory properties, some of which may be carried out by MSCs-secreted EVs.[49] MSCs originated from the umbilical cord, adipose tissue, bone marrow, gingival tissue, and periosteum played a key role in regulating synovial cells function and remodeling synovial microenvironment.[9] Emerging evidence showed that MSCs-derived EVs (MSCs-EVs) were more effective and less toxic in treating RA than MSCs.[50] Experimental results indicated that MSCs-EVs internalization by FLSs, macrophages, and chondrocytes may have an inhibitory effects on FLSs proliferation, chondrocyte apoptosis, inflammatory mediator release, and osteoclast differentiation, thereby hindering RA progression.[51]

It was reported that bone marrow mesenchymal stem cells (BMSCs) effectively alleviated joint inflammation in RA pigs.[52] Another study confirmed the efficacy of BMSCs-derived EVs in attenuating RA symptoms by inhibiting proliferative and inflammatory phenotypes.[53] Human umbilical cord MSCs (hUCMSCs)-derived EVs relieved synovial inflammation by elevating Treg/Th17 ratio and IL-10 level, displaying better therapeutic efficacy against RA than hUCMSCs or methotrexate.[54] It was also suggested that hUCMSC-EVs had a pronounced effect on reliving RA symptoms by rebalancing Th17/Treg ratio, repressing lymphocyte proliferation and upregulating Foxp3 mRNA.[55] Gingival MSCs (GMSCs)-derived EVs can affect pro-inflammatory factors and macrophage polarization, which may represent a cell-free treatment strategy for RA.[56] Adipose-derived stem cells (ADSCs)-derived EVs reproduced immunomodulatory functions and overcame the limitation of cell therapy.[57] Although ADSCs-EVs were more effective in inducing cartilage and bone regeneration than BMSC-EVs,[58] the potential role of ADSCs-EVs in the modulation of immune-suppression, Treg/Th17 ratio, and macrophage polarization kept discordant.[59] Granulocytic myeloid-derived suppressor cells (G-MDSCs)-derived EVs could alleviate the malignant phenotypes of collagen-induced arthritis (CIA) mice by inhibiting Th1/Th17 cell differentiation, promoting anti-inflammatory cytokine (IL-10) secretion, and increasing the proportion of Treg cells.[60]

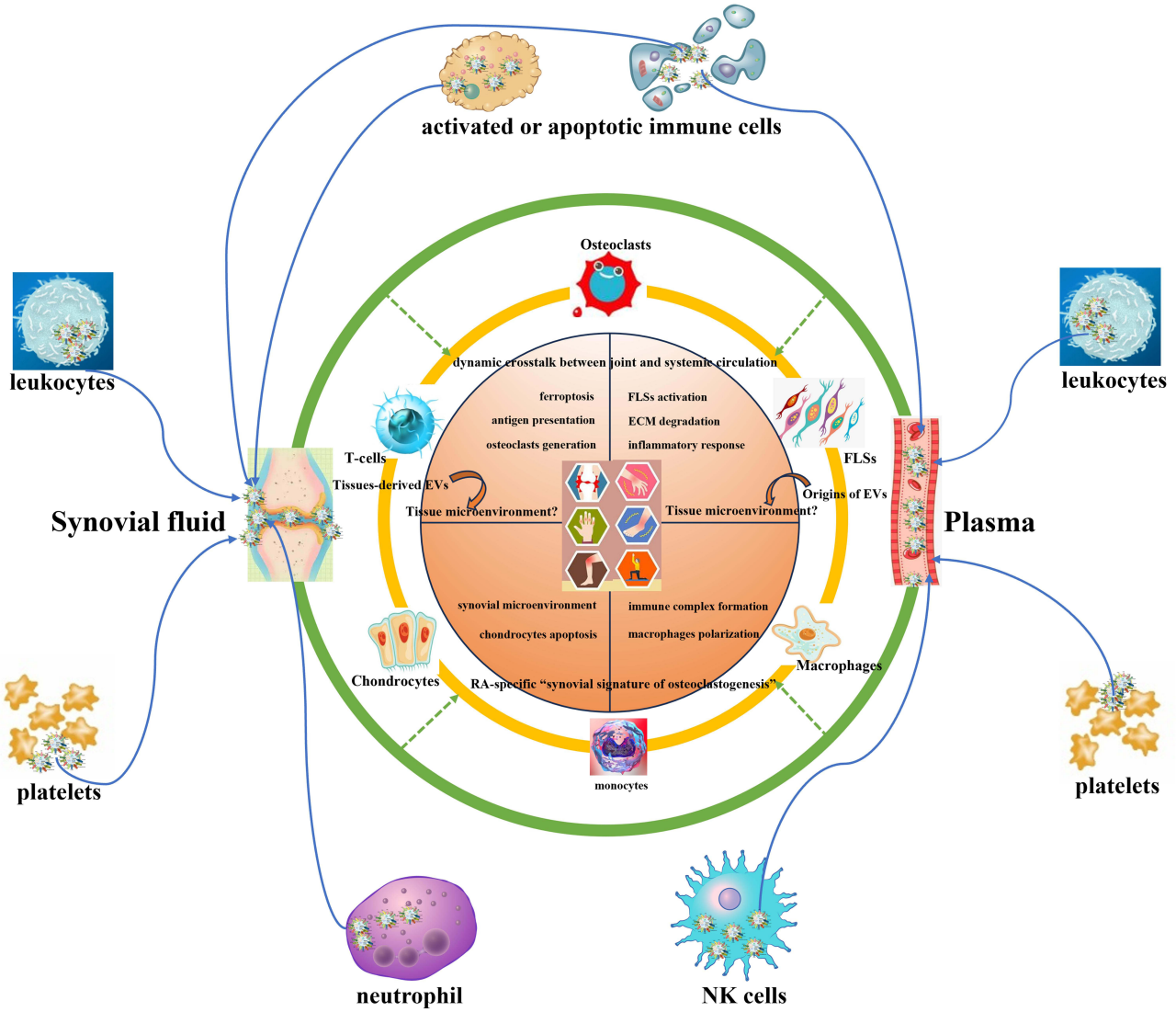


Figure 1 The origins of EVs that existed in the circulation and synovial fluid of RA individuals, and dysregulated EVs-mediated phenotypic changes in RA.

It was suggested that polymorphonuclear neutrophil-derived EVs (PMN-EVs) can induce ECM deposition, inhibit chondrocyte apoptosis, and reduce the secretion of prostaglandin E2 and IL-8. PMN-EVs were able to suppress macrophages-FLSs crosstabs and neighboring FLSs activation, mitigating cartilage degradation and bone erosion.[38] However, in another study, neutrophil-derived EVs were shown to have no regulatory effect on immune response.[61] Inspired by anti-inflammatory properties and chemotaxis of neutrophils, ultrasmall Prussian blue nanoparticles (uPB-Exos), known as biomimetic EVs, were developed to selectively accumulate in activated FLSs, neutralizing pro-inflammatory factors and clearing reactive oxygen species.[62] Metabolically engineered stem cells-derived EVs could accumulate in inflamed joint and reprogram synovial microenvironment, exhibiting great potential as next-generation therapeutic drugs for RA.[63] (Figure 2)

Potential Roles of Exosomal ncRNAs in RA

The specific mechanism of EVs' involvement in pathogenesis of RA has not been fully elucidated. Thus far, a growing number of studies have concentrated on the causal relationship between RA and exosomal ncRNAs such as circular RNAs (circRNAs), long non-coding RNAs (lncRNAs) and microRNAs (miRNAs), with a view to investigating the predictive and diagnostic role of exosomal ncRNAs in RA (Figure 3), as well as promising therapeutic targets.

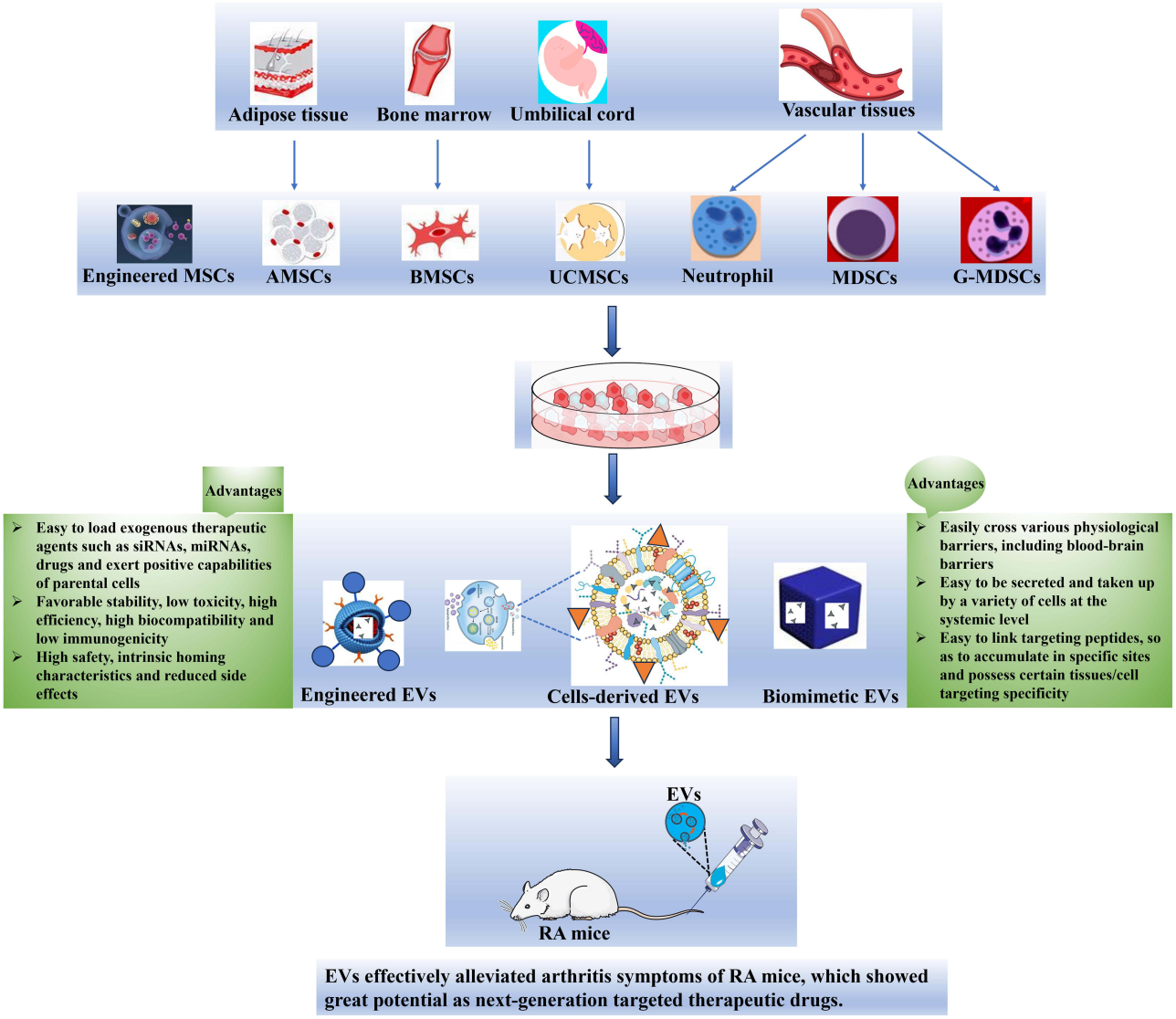


Figure 2 MSCs-derived EVs, biomimetic EVs and engineered EVs are expected to make breakthroughs in the treatment of RA.

Exosomal circRNAs and Their-Mediated Mechanisms in RA

CircRNAs, a special type of ncRNAs with a covalently closed ring structure, are formed by reverse splicing and largely exist in cytoplasm or exosomes, where they are not easily degraded by exonucleases.[64,65] There is increasing evidence that exosomal circRNAs functioned as efficient sponges of miRNAs that affect target mRNAs, thus participating in the pathogenesis of RA (Table 1). An original study showed that the expression of serum exosomal circFBXW7 in RA patients was lower than that in HCs. Reduced level of exosomal circFBXW7 delivered into FLSs may promote FLSs proliferation, invasion, and migration via the upregulation of miR-216a-3p and the repression of HDAC4, thus exacerbating RA progression.[66] It was speculated that depressed expression of exosomal circEDIL3 may accelerate RA progression due to insufficient delivery of circEDIL3 to recipient FLSs. Competitive endogenous RNAs (ceRNAs) (Exos-CircEDIL3/miR-485-3p/PIAS3) network can activate STAT3 to induce VEGF transcription, which may be a core mechanism for RA.[67] A recent study revealed that FLSs-derived exosomal circFTO was evidently elevated in RA patients compared to HCs. Mechanistically, exosomal circFTO can hinder chondrocytes proliferation, migration and anabolism in a m6A-dependent manner by decreasing SOX9 expression.[68]

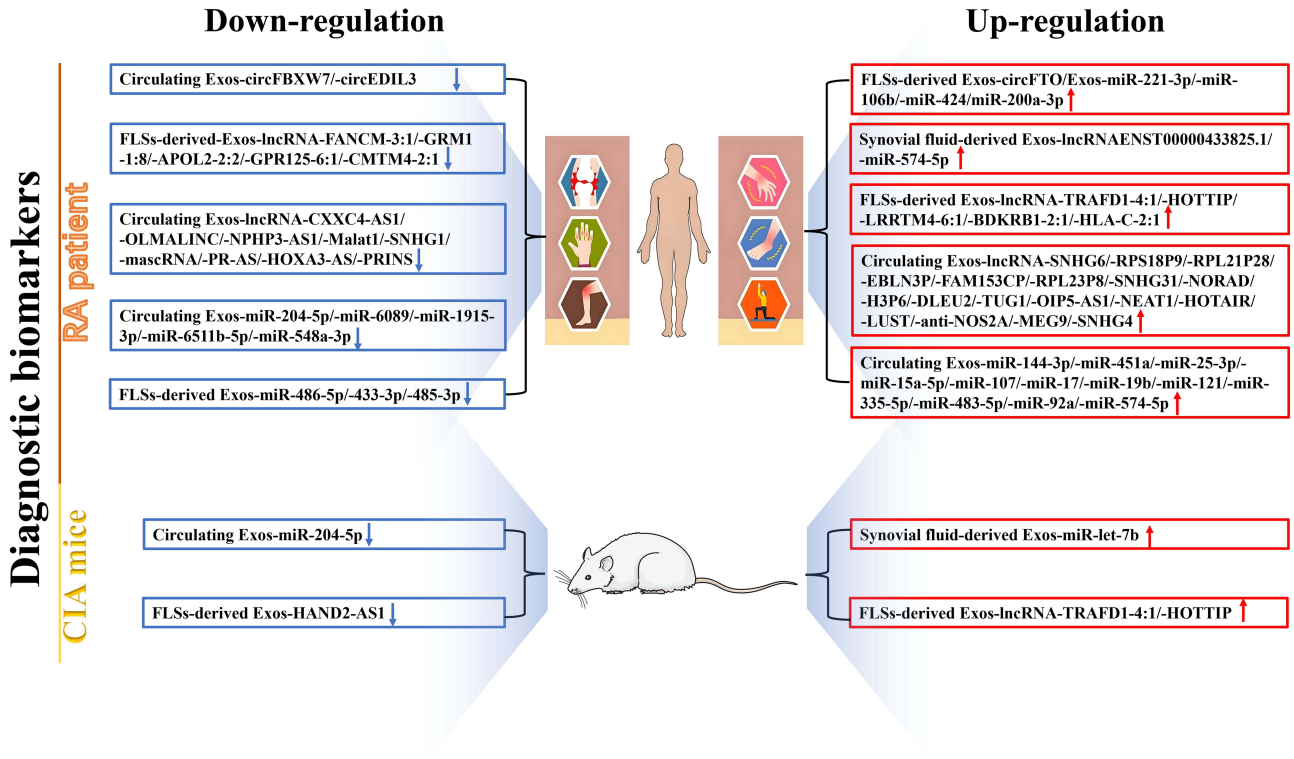


Figure 3 Dysregulated expression of ncRNAs (circRNAs, lncRNAs, miRNAs) may serve as promising diagnostic biomarkers of RA.

Exosomal lncRNAs and Their-Mediated Mechanisms in RA

Long noncoding RNAs (lncRNAs) are a class of single-stranded ncRNAs with a length of longer than 200 nucleotides.[76,77] Several studies have proposed that exosomal lncRNAs are crucial for the execution of biological functions of SFs, macrophages and chondrocytes.[78,79] It was found that dysregulation of exosomal lncRNAs are strongly correlated with the progression of RA. (Table 1)

Circulating Exosomal lncRNAs in RA

Circulating exosomal lncRNAs are easily detectable and can be utilized as minimally invasive biomarkers for monitoring RA. Song et al found that serum exosomes from RA patients had notably reduced levels of lncRNA Malat1, SNHG1, mascRNA, PR antisense, HOXA3as, and PRINS, and elevated levels of lncRNA HOTAIR, LUST, anti-NOS2A, MEG9, SNHG4, TUG1, and NEAT1. They indicated that decreased HOTAIR expression in synoviocytes may be responsible for the activation of MMP-2 and MMP-13, causing cartilage matrix dissolution and joint destruction.[69] Rao et al reported that the serum exosomal lncRNA NEAT1 was upregulated in RA patients, which may promote the proliferation and inflammation of FLSs by modulating miRNA-23a/MDM2/SIRT6 axis. It was found that lncRNA NEAT1 mimics-loaded PBMCs-derived exosomes from RA patients could increase paw thickness and arthritis score of mice.[70] A clinical evaluation showed that serum exosomal lncRNA NEAT1 expression visibly increased in RA patients in comparison to HCs. Mechanistic studies revealed that exosomal lncRNA NEAT1 supported $CD4^{+}$T cell proliferation and Th17 cell differentiation by regulating miR-144-3p/ROCK2/WNT axis.[71] Plasma exosomal SNHG6, RPS18P9, RPL21P28, EBLN3P, FAM153CP, RPL23P8, SNHG31, NORAD, H3P6, DLEU2, TUG1 and OIP5-AS1 were upregulated in RA patients, whereas CXXC4-AS1, OLMALINC, and NPHP3-AS1 were downregulated. The area under the curve of these candidate lncRNAs ranged from 0.847 for OLMALINC to 0.994 for CXXC4-AS1.[12]

Synovial Fibroblasts-Derived Exosomal lncRNAs in RA

Excessive activation of SFs is the main pathological hallmark of RA.[80] Yao et al found that lncRNA HOTTIP shuttled by

Table 1 Dysregulation of Exosomal circRNAs and lncRNAs in RA Individuals

Symbols (Exosomal ncRNAs)	Sources	Relative expression	Recipients	Targets	Phenotypic changes	References
CircRNA-FBXW7	Serum	Down	FLSs	miR-216a-3p/HDAC4	Proliferation, migration and inflammation	[66]
CircRNA-EDIL3	Serum	Down	FLSs	miR-485-3p/PIAS3/ STAT3/VEGF	Angiogenesis	[67]
CircRNA-FTO	FLSs	Down	Chondrocytes	SOX9	Proliferation, migration, anabolism	[68]
LncRNA-HOTAIR	Serum	Up	Macrophages, Osteoclasts, FLSs	MMP-2/MMP-13	Bone and cartilage matrix dissolution	[69]
LncRNA-NEAT1	PBMCs	Up	FLSs	miRNA23a/ MDM2/SIRT6	Cell viability and inflammation	[70]
LncRNA-NEAT1	Serum	Up	CD4+T cells, Th17 cells	miR-144-3p/ROCK2/WNT	Proliferation, differentiation and migration	[71]
LncRNA-HOTTIP	FLSs	Up	Th17/Treg cells	miR-1908-5p/STAT3	Inflammation	[72]
LncRNA-TRAFD1-4:1	FLSs	Up	Chondrocytes	miR-27a-3p/ CXCL1	Proliferation, migration and cartilage extracellular matrix	[73]
LncRNA-HAND2-AS1	Unknown	Down	FLSs	miR-143-3p/TNFAIP3	Proliferation, motility and inflammation	[74]
ENST00000433825.1	Synovial fluid	Up	Unknown	Unknown	CRP level	[75]

SFs-derived exosomes promoted inflammation by regulating miR-1908-5p/STAT3 axis and Th17/Treg proportion, exerting an expansionary role in the pathogenesis of RA.[72] In view of lacking an in vivo microenvironment, RASFs were treated with TNF-α to mimic inflammatory conditions.[81] It was found that the expression of exosomal lnc-TRAFD1-4:1, lnc-LRRTM4-6:1, lnc-BDKRB1-2:1 and lnc-HLA-C-2:1 derived from TNF-α-treated RASFs were significantly higher than those of non-TNF-α-treated RASFs. However, the expression of exosomal lnc-FANCM-3:1, lnc-GRM1-1:8, lnc-APOL2-2:2, lnc-GPR125-6:1 and lnc-CMTM4-2:1 was visibly lowered in TNF-α-stimulated RASFs. RASFs-derived exosomal lncRNA TRAFD1-4:1 may increase CXCL1 expression by competitively sponging miR-27a-3p, thus preventing chondrocytes proliferation and migration.[73] LncRNA-HAND2-AS1 was markedly underexpressed in RASFs, indicating the involvement of HAND2-AS1 in RA.[82] Another study emphasized that the intercellular transfer of exosomal HAND2-AS1 and subsequent regulation of miR-143-3p/TNFAIP3 axis may be involved in the course of RA.[74] It was showed that synovial fluid-derived exosomal ENST00000433825.1 was highly and uniquely expressed in RA patients in comparison to OA or gout patients, exhibiting a positive correlation with CRP level.[75]

Exosomal miRNAs and Their-Mediated Mechanisms in RA

miRNAs, a group of highly conserved endogenous short-chain ncRNAs, can negatively regulate gene expression at the post-transcriptional level by binding to the complementary 3'-UTR of target mRNAs.[83,84] Owing to high abundance and good stability, exosomal miRNAs are extremely beneficial for the diagnosis and prognosis of RA. (Table 2)

Circulating Exosomal miRNAs in RA

Wu et al identified 14 abnormally expressed plasma exosomal miRNAs in RA patients. The abundance of plasma exosomal miR-204-5p was visibly reduced in both RA patients and CIA mouse, and was negatively correlated with RA parameters. Mechanistic studies revealed that the reduction of T lymphocyte-released exosomal miR-204-5p internalized by SFs led to increased expression of CRKL and ANGPT1, promoting FLSs proliferation and invasion.[85] Serum exosomal miR-6089 from RA patients was significantly decreased compared to HCs, and was inversely related to CRP, RF and ESR. It was indicated that downregulation of exosomal miR-6089 was followed by the activation of TLR4, which promoted inflammatory cascade of macrophages-like THP-1 cells.[86] The miRNA array and qRT-PCR analysis on Korean RA patients demonstrated that the expression levels of serum exosomal miR-1915-3p/-6511b-5p of the clinical response (CR) group were significantly greater than those of non-CR group.[87] Another study showed that serum exosomal miR-144-3p, −451a, −25-3p, −15a-5p, and −107 were upregulated in early RA patients compared to HCs, accompanied by decreased expression of the common target gene YHWAB. Bioinformatics analysis revealed that a novel serum biomarker panel composed of Exos-miR-451a/-miR-25-3p and soluble TWEAK could differentiate early RA patients with 95.8% accuracy, which was 2.9% higher than diagnostic value of ACPA.[88] Differential analysis on miRNAs profiles suggested that the expression levels of circulating exosomal miR-17, miR-19b, and miR-121 in RA patients were relatively higher than those in HCs, with exosomal miR-17 inversely correlating with Treg frequency. In-depth studies indicated that exosomal miR-17 may disturb the induction of Tregs by decreasing TGFBR II expression, contributing to the development of RA.[89] It was found that serum exosomal miR-548a-3p was downregulated in RA patients, and was negatively correlated with serum CRP, RF, and ESR levels. Molecular experiments suggested that exosomal miR-548a-3p may be involved in the pathogenesis of RA by regulating proliferation and activation of pTHP-1 cells in a TLR4/NF-κB signaling pathway-dependent manner.[90] Small RNAs sequencing revealed that the expression levels of circulating exosomal miR-335-5p and miR-483-5p in RA patients were significantly greater than those in HCs. Moreover, miR-483-5p expression was positively correlated with anti-CCP, ESR, CRP, and RF levels, which may be a reliable indicator for predicting RA activity and severity.[91] An opposite perspective was that plasma exosomes in RA patients do not have the ability to promote cell proliferation, but can prevent cell apoptosis and increase the release of TNF-α and IL-1β. In particular, exosomal miR-92a was distinctly overexpressed in bone destruction group.[102] Gong et al demonstrated a noteworthy upregulation of serum exosomal miR-885-5p, miR-6894-3p, and miR-1268a in the RA patients compared to HCs, which may be employed as early diagnostic and predictive biomarkers for RA.[92]

Table 2 Dysregulated Expression of Exosomal miRNAs in RA Individuals

Symbols (Exosomal miRNAs)	Sources	Relative expression	Recipients	Targets	Phenotypic changes	References
miR-204-5p	Plasma	Down	FLSs	CRKL, ANGPT1	Proliferation, invasion	[85]
miR-6089	Plasma	Down	THP-1 cells	TLR4	Proliferation, activation and inflammation	[86]
miR-1915-3p/-6511b-5p	Serum	Up	Unknown	Unknown	Unknown	[87]
miR-451a/-25-3p	Serum	Down	Unknown	YWHAB	Unknown	[88]
miR-17	Plasma	Up	Treg cells	TGFBR II	Differentiation, induction	[89]
miR-548a-3p	Serum	Down	Pthp-1 cells	TLR4/NF-κB	Proliferation, activation and inflammation	[90]
miR-335-5p/-483-5p	Plasma	Up	Synovial tissues	SRSF4	Unknown	[91]
miR-885-5p/-6894-3p/-1268a	Serum	Up	Unknown	Unknown	Unknown	[92]
miR-155-5p/-146a-5p/-323a-5p/-1307-3p	MH7A	Up	T-cells, osteoclasts	CD6 NDRG2	T-cells activation, osteoclast inhibition	[93]
miR-424	RASFs	Up	T cells	FOXP3	Differentiation and dysregulation of TH17/Treg ratio	[94]
miR-106b	RASFs	Up	Cartilage tissues and chondrocytes	PDK4	Proliferation and migration	[95]
miR-221-3p	SFs treated with TNF-α	Up	Osteoblasts	Dkk2	Differentiation and mineralization	[96]
miR-574-5p	Synovial fluid	Up	Osteoclasts, CD14+ monocytes	TLR 7/8	Differentiation, maturation and inflammation	[97]
miR-103a	RAW264.7 cells	Up	FLSs	HNF4α, JAK/STAT3	Inflammation and angiogenesis	[98]
miR-let-7b	Synovial fluid	Up	Macrophages	TLR7	M1 macrophages activation	[99]
miR-486-5p/-433-3p/-485-3p	RASFs	Down	HDMECs	VEGF/FOXO1	Migration and tube formation	[47]
miR-124-3p	RASFs	Down	Macrophages	PTX3	Activation and migration	[100]
miR-200a-3p	RASFs	Up	HUVECs	KLF6/VEGFA	Migration, invasion, and angiogenesis	[101]

Synovial Fibroblasts-Derived Exosomal miRNAs in RA

Differential analysis identified 4 upregulated exosomal miRNAs (miR-155-5p, miR-146a-5p, miR-323a-5p, and miR-1307-3p) in TNF-α-stimulated MH7A cells. It was speculated that miR-323a-5p reduced T cell activation signal by targeting CD6, while miR-1307-3p suppressed osteoclast-related gene expression by specifically binding to NDRG2.[93] A parallel study showed that a hypoxic microenvironment existed in the synovium of RA patients, which may result in an increased expression of exosomal miR-424 and decreased FOXP3 expression in RASFs. Exosomal miR-424 may disrupt TH17/Treg homeostasis and aggravate RA phenotypes.[94] miR-106b was overexpressed in RASFs-derived exosomes, and exosomal miR-106b can be transferred into chondrocytes, thus restricting their migration and proliferation by modulating PDK4/RANKL/RANK/OPG axis.[95] Maeda et al reported that TNF-α treatment enhanced the secretion of exosomal miR-221-3p in SFs. Mechanistically, overexpression of miR-221-3p had a baffled effect on the differentiation and mineralization of osteoblasts, affecting articular erosion and bone formation by negatively regulating Dkk2 at erosion sites.[96] Hegewald et al suggested that elevated level of exosomal miR-574-5p derived from synovial fluid and serum of RA patients promoted osteoclast differentiation and maturation, which may be attributed to the activation of TLR 7/8 signal.[97] High abundance of exosomal miR-103a and low expression of HNF4α in RAW264.7 cells were synchronously detected in RA mice. There is evidence that exosomal miR-103a may promote inflammation and angiogenesis by downregulating HNF4A and activating JAK/STAT3 pathway in SFs.[98] Kim et al demonstrated that exosomes containing miR-let-7b could transform RA/mouse primary macrophages (M0) or anti-inflammatory macrophages (M2) into inflammatory macrophages (M1) via the TLR-7 junction, thus aggravating arthritis. In particular, these phenotypic changes were not found in TLR7-deficient mice.[99] The expression of exosomal miR-486-5p, miR-433-3p and miR-485-3p from SFs were repressed after ferroptosis, provoking angiogenesis and migration by inducing VEGF expression and tube formation.[47] Macrophages activation and migration may be causally related to low expression of RASFs-derived exosomal miR-124 and high PTX3 expression.[100] The expression of miR-200a-3p was significantly increased in exosomes derived from TNF-α-stimulated RASFs and in exosomes-treated HUVECs compared to non-TNF-α-stimulated RASFs. It was confirmed that exosomes derive from TNF-α-treated FLSs may enhance HUVECs cell migration, invasion, and angiogenesis through miR-200a-3p/KLF6/VEGFA axis.[101]

Therapeutic Effect of Exosomal ncRNAs on RA

In recent years, a series of abnormally expressed exosomal ncRNAs have been considered to be candidate therapeutic targets. The potential therapeutic effects of gene therapy reagents using exosomes from different origins as targeted delivery vectors on CIA mice have been extensively studied (Figure 4).

Exosomal circRNAs in the Treatment of RA

Considering that exosomes-wrapped circRNAs can be delivered to recipient cells, exosomal circRNAs may be valuable therapy reagents for RA. BMSCs-derived exosomal circFBXW7 may be internalized into FLSs, inhibiting proliferation and migration of FLSs. Exosomal circFBXW7 competitively sponged miR-216a-3p to upregulate HDAC4, and exerted a restraining effect on the progressive phenotypes and inflammatory responses.[66] In vitro results showed that SMSCs-derived exosomal circEDIL3 (Ad-circEDIL3-SMSCs Exos) downregulated VEGF expression via miR-485-3p/PIAS3/STAT3 axis, suppressing angiogenesis and pannus formation. Furthermore, injection of SMSCs-derived exosomal circEDIL3 had a stronger ability to ameliorate arthritis than SMSCs-derived exosomes alone.[67] Administration of AAV5/sh-circFTO evidently reduced arthritis symptoms in CIA-induced mice by reversing SOX9 expression, but there have been no relevant studies using exosomes as targeted vectors for sh-circFTO delivery. (Figure 5)

Exosomal lncRNAs in the Treatment of RA

Lentivirus-mediated HOTAIR upregulation suppressed the expression of MMP-2 and MMP-13 in synoviocytes, suggesting that exosomal HOTAIR may have a positive therapeutic effect on RA once they possess synovium-targeting specificity.[69] The inflammatory cytokine level and cell viability of RASFs co-cultured with PBMCs-derived exosomes transfected with sh-NEAT1 were decreased. Moreover, injection with sh-NEAT1-loaded PBMCs-derived exosomes resulted in a reduction of lncRNA NEAT1 transferred to synovial tissue, thus preventing RA deterioration by regulating

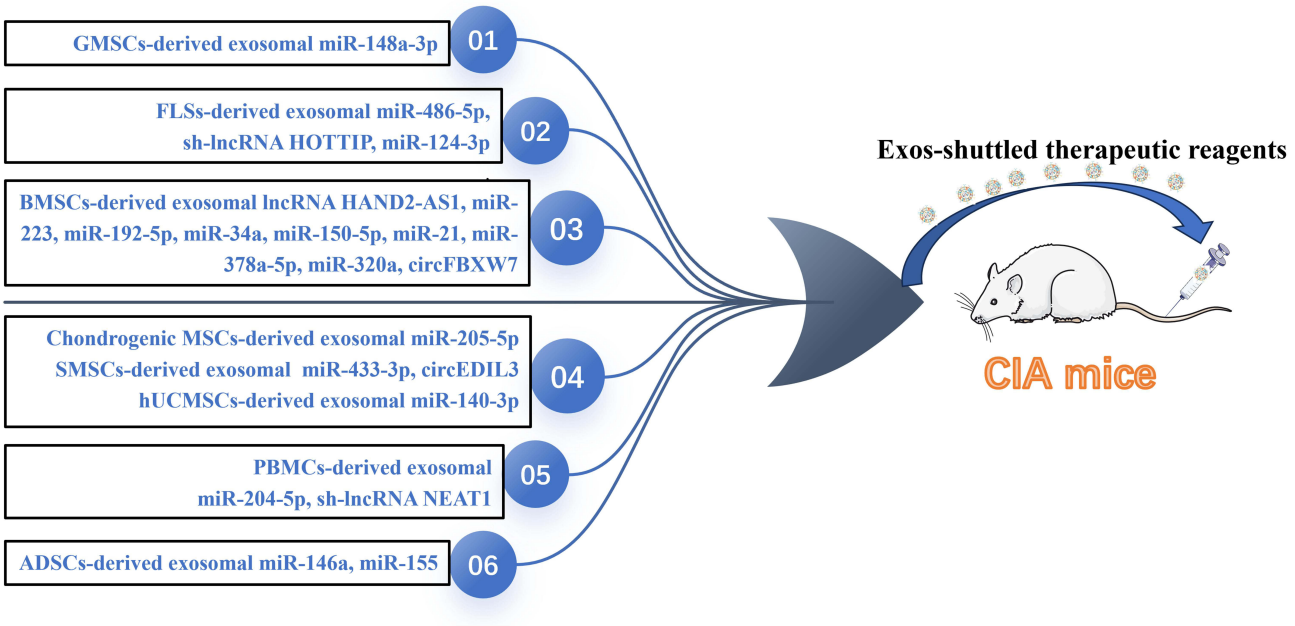


Figure 4 A series of dysregulated exosomal ncRNAs have been developed to be candidate therapeutic targets. The therapeutic effects of gene therapy reagents using exosomes as targeted delivery vectors on CIA mice.

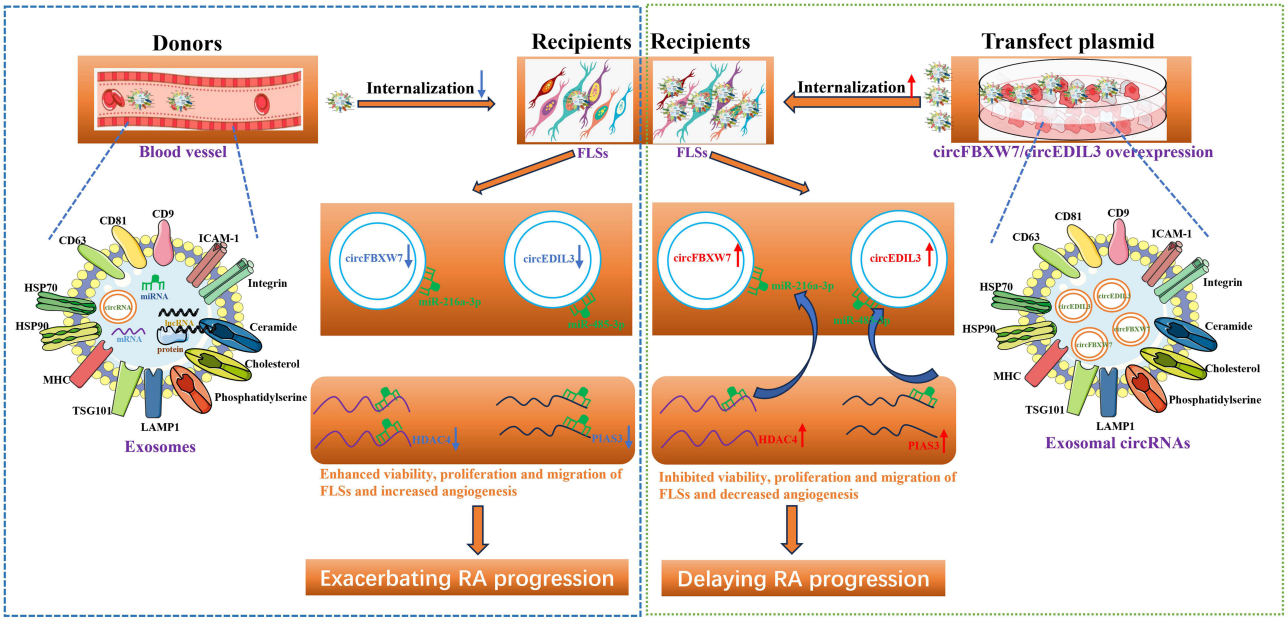


Figure 5 (Left) Dysregulation of circRNAs may be involved in the pathogenesis of RA. (Right) Exos-shuttled gene therapy reagents targeting candidate circRNAs could delay the progression of RA progression.

the miR-23a/MDM2/SIRT6 axis.[70] It was revealed that serum-derived exosomes from RA patients can induce the proliferation and differentiation of CD4+T cells and aggravate the morbidity of CIA mice, whereas the addition of sh-NEAT1 could be beneficial in improving RA symptoms. Exosomes treatment alone or in combination with sh-NEAT1 and miR-144-3p mimics were delivered efficiently to synoviocytes, which may be an effective therapeutic strategy for RA via regulation of miR-144-3p/ROCK2/WNT pathways.[71] CIA mice transfected with either lncRNA HOTTIP knockout or miR-1908-5p overexpression reagent had alleviated symptoms. Yao et al highlighted that knockout agent

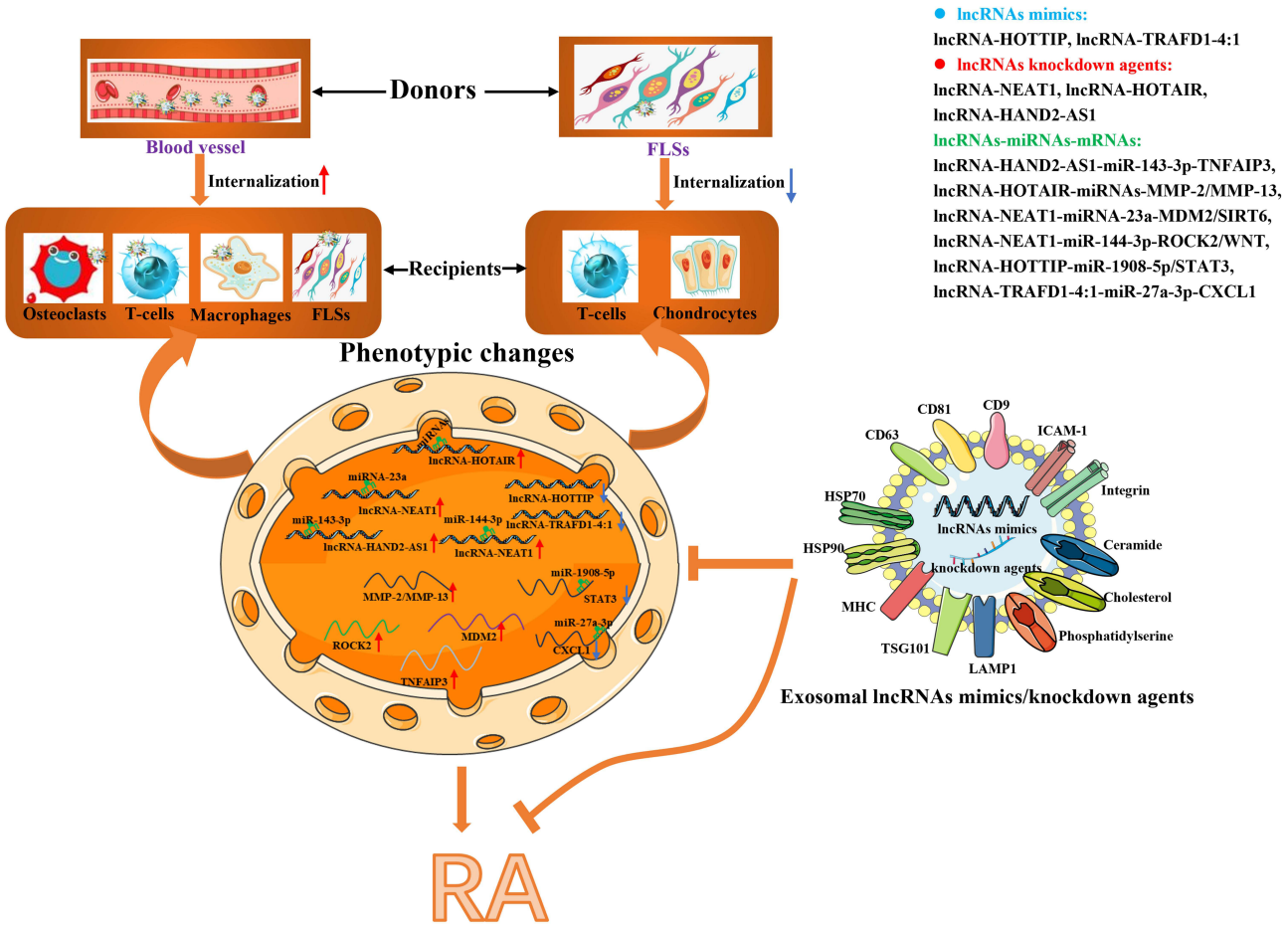


Figure 6 Exos-shuttled gene therapy reagents exerted a significant therapeutic effect on RA by mimicking or silencing candidate lncRNAs.

of lncRNA HOTTIP shuttled by FLSs-derived exosomes can rescue RA deterioration via miR-1908-5p/STAT3 axis.[72] Silencing lnc-TRAF1-4:1 promoted chondrocytes proliferation and migration. It was speculated that exosomes-carried lnc-TRAF1-4:1 knockout reagent transferred into chondrocytes may have a protective effect against cartilage impairment and bone erosion.[73] Su et al indicated that BMSCs-derived exosomal lncRNA HAND2-AS1 played an active role in alleviating the malignant biological behavior (excessive proliferation and inflammation) of RASFs by modulating miR-143-3p/TNFAIP3/NF-κB axis.[74] (Figure 6)

Exosomal miRNAs in the Treatment of RA

Down-regulating SFs-derived exosomal miR-424 prevented RA deterioration by elevating FOXP3 expression and rebalancing Treg/Th17 ratio.[94] In vitro study showed that exogenous inhibition of exosomal miR-106b led to a reduced amount of miR-106b internalized into chondrocytes, thereby promoting their proliferation and migration via the upregulation of PDK4. Injection of miR-106b-antagomir exerted an unexpected role in relieving symptoms of CIA mice.[95] It was proposed that exosomal miR-574-5p inhibitor may act as both a prostaglandin synthesis regulator and a TLR7/8 ligand, thus alleviating the arthritis symptoms of RA.[97]

After injection of BMSCs-derived exosomal miR-192-5p, the arthritis scores, joint destruction, and inflammatory responses were visibly alleviated, indicating the therapeutic effect of exosomal miR-192-5p on RA by silencing RAC2.[103] It was reported that a high abundance of exosomal miR-34a carried by BMSCs relieved RA symptoms by binding to cyclin I and activating ATM/ATR/p53 signaling pathway in RASFs. Conversely, the reduction of miR-34a may weaken the protective effect of BMSCs-derived exosomes on RA rats.[104] It was showed that miR-205-5p carried by chondrogenic MSCs-exosomes had an inhibitory effect on the inflammatory and proliferative phenotypes of IL-1β-

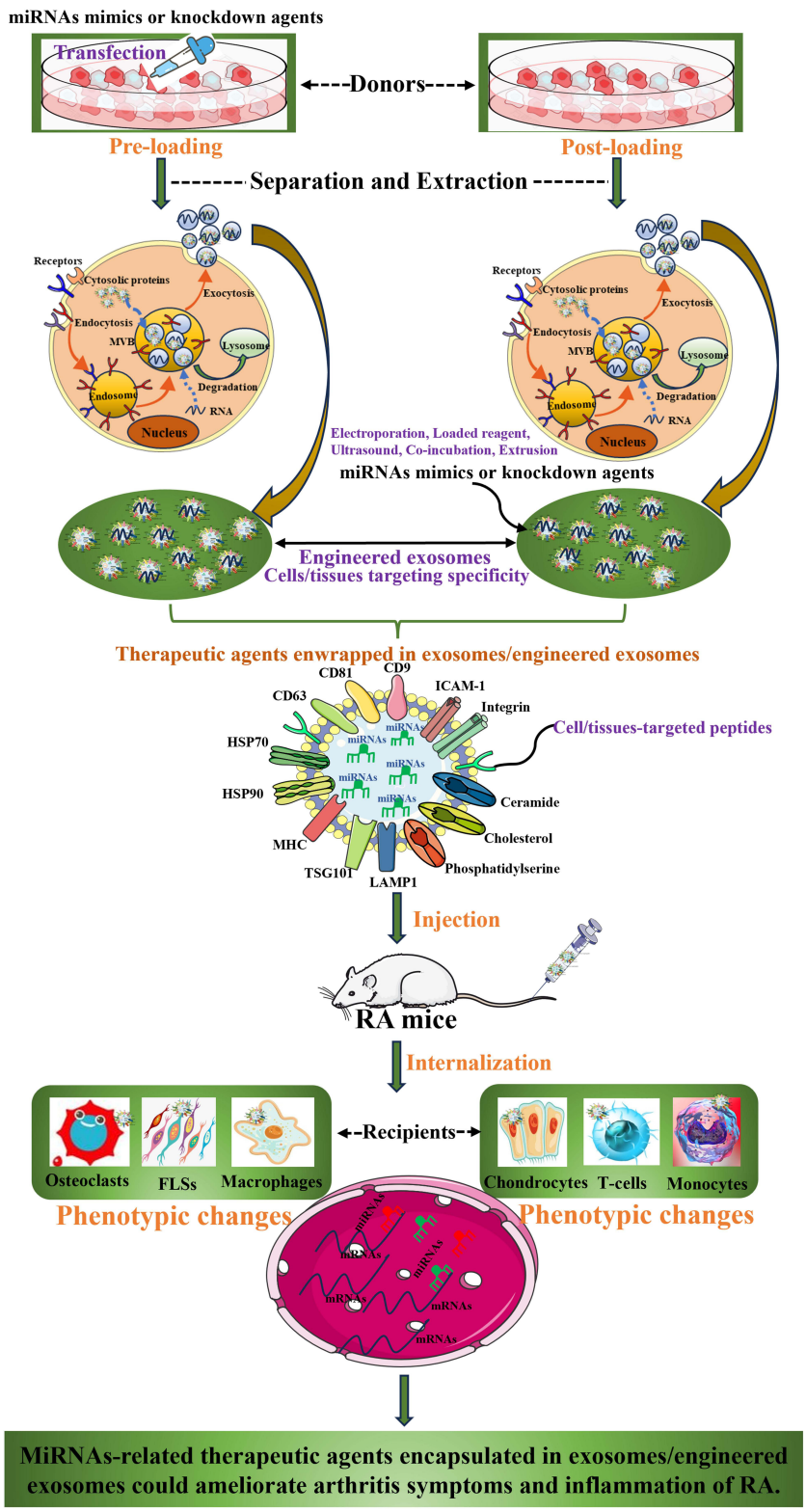
treated RASFs and arthritis symptoms of CIA mice, which depended on MDM2 downregulation and regulation of MAPK and NF-κB pathways.[105] A previous study revealed that hUCMSC-derived exosomal miR-140-3p can inhibit chondrocytes apoptosis and decelerate FLSs proliferation by inhibiting SGK1, thereby alleviating joint destruction of RA rats.[106] Experimental evidence supported that exosomal miR-150-5p inhibited the migration and invasion of RASFs and tube formation of HUVECs by decreasing MMP14 and VEGF expression, reducing posterior paw thickness and clinical arthritis scores of CIA mice.[107] Human MSCs-derived exosomal miR-124a can suppress proliferation and migration of MH7A cells and induce apoptosis.[108] Huang et al found that BMSCs-derived exosomes carrying highly expressed miR-223 could be delivered into RAW264.7, thus alleviating RA symptoms through the inactivation of NLRP3 inflammasome.[109] Another original study suggested that high level of BMSCs-derived exosomal miR-21 can be delivered into RASFs, relieving RA symptoms by regulating TET1/KLF4 axis.[110] BMSCs-carried exosomal miR-320a accumulated in RASFs and inhibited their migration, proliferation, and inflammation by silencing CXCL9. In vivo results showed that exosomal miR-320a exerted a positive effect on alleviating arthritis symptoms in CIA mice.[111] Transfection of ADSCs with a plasmid carrying miR-146a/miR-155 efficiently generated ADSCs-derived exosomal miR-146a/miR-155, exerting an inhibitory effect on RA phenotypes.[112]

It was reported that human T lymphocytes-derived exosomes containing a high abundance of miR-204-5p can be efficiently delivered into RASFs, thus inhibiting the activation of FLSs and alleviating the arthritis severity of CIA mice.[85] It was found that TLR4 expression was reduced when THP-1 cells were co-incubated with exosomes-coated high abundance of miR-6089, suggesting the therapeutic effect of exosomal miR-6089 on RA.[86] It was speculated that miR-548a-3p shuttled by exosomes might restrain the positive feedback between malignant proliferation and inflammation by regulating LPS/TLR4-NF-κB/P65-mediated inflammatory response, thereby exerting a protective role in RA.[90] The fusion of FLSs-secreted exosomal miR-221 with chondrocytes may lead to RA phenotypes. Downregulation of miR-221 in FLSs-derived exosomes favored the proliferative activity of chondrocytes and inhibited inflammatory responses, which may be causally related to the enhancement of TLR4-MYD88 signal transduction.[113] Upregulation of miR-486-5p in RASFs-derived exosomes activated the BMP/Smad signaling pathway in osteoblasts, thus promoting osteoblast differentiation and alleviating arthritis severity.[42] It was also showed that SMSCs-shuttled exosomal miR-433-3p inhibited angiogenesis by regulating FOXO1/VEGF axis, thereby attenuating RA symptoms.[47] Nakamachi et al found that RASFs-derived exosomal miR-124-3p suppressed macrophages migration by silencing PTX3 without affecting inflammatory cytokines level.[100] BMSCs-derived exosomes containing miR-378a-5p can be transferred into human synovial microvascular endothelial cells to delay RA progression by inactivating the IRF1/STAT1 axis.[114] GMSCs-derived exosomal miR-148a-3p restored Treg/Th17 ratio via IKKB/NF-κB axis, impeding RASFs invasion and cartilage destruction, which indicated the potential therapeutic efficacy on RA.[115] (Figure 7)

Concluding Remarks and Perspectives

Classical theories may be insufficient to explain the pathogenesis of RA, while avant-garde theories will bring a new dawn for the diagnosis and therapy of RA. Exosomes, as star carriers, established a unique interactive system to participate in biological processes or realize targeted drug delivery by transmitting nucleic acids, proteins, cholesterol, and others.[116] Several points deserve further consideration. The number of RA individuals and HCs is not large enough, which may lead to inconsistent results due to unexpected errors and lack of quality control. Relevant studies on exosomal ncRNAs in predicting treatment response to DMARDs in RA patients are extremely scarce. Establishing effective and under-effective treatment groups in RA patients to identify biomarkers for efficacy prediction may be a future research direction. Although epigenetic modifications of RA synovial chondrocytes and macrophages have been well studied,[117,118] the role of their-originated exosomes in RA remains unknown. Single-cell RNA sequencing (scRNA-seq) can not only analyze cell heterogeneity and define cell types at the single-cell level, but also may be conducive to better understand transcriptional dynamics and epigenetic regulation during RA progression. Tissue-originated exosomes combined with scRNA-seq could consider cell heterogeneity and intercellular communication in synovial microenvironment, which may provide a direction for the exploration of diagnostic and therapeutic indicators for RA.

Since RASFs show malignant proliferative properties similar to those of tumor cells, exosomal ncRNAs derived from or taken up by tumor cells may also provide a meaningful reference for the diagnosis and therapy of RA. Exosomal



- **miRNAs mimics:**

miR-204-5p, miR-6089, miR-548a-3p, miR-486-5p, miR-433-3p, miR-192-5p, miR-34a, miR-205-5p, miR-140-3p, miR-150-5p, miR-124a,miR-223, miR-21, miR-320, miR-146a, miR-155

- **miRNAs knockdown agents:**

miR-221, miR-124-3p, miR-424, miR-106b, miR-574-5p

- **miRNAs-mRNAs pairs:**

miR-424-FOXP3, miR-106b-PDK4
miR-574-5p-TLR7/8, miR-192-5p-RAC2
miR-34a-cyclin I, miR-205-5p-MDM2
miR-140-3p-SGK1, miR-150-5p-MMP14/VEGF
miR-223/NLRP3, miR-21-TET1
miR-320-CXCL9, miR-146a-FOXP3
miR-204-5p-CRKL/ ANGPT1, miR-155-RORγT
MiR-548a-3p-TLR4/NF-κB, miR-6089-TLR4
miR-221-TLR4/MYD88, miR-486-5p-Tob1
miR-433-3p-VEGF/FOXO1, miR-124-3p-PTX3

Figure 7 MiRNAs mimics or inhibitors shuttled by exosomes/engineered exosomes can ameliorate RA symptoms by specifically targeting candidate biomarkers.

ncRNAs-mediated communication among FLSs, macrophages, and chondrocytes has been associated with the progression of OA, provide inspiration for RA research. Notably, inconsistent results may be acceptable in global studies due to significant population differences. With the support of big data, some parameters can be comprehensively calculated to obtain a panel of biomarkers applicable to a certain population to effectively distinguish RA patients from HCs and assess disease activity.

Biomimetic/engineered exosomes have been shown to significantly accumulate in arthritic sites, ameliorating the overall arthritis severity in CIA mice, which exhibited a greater capability in the clinical treatment of RA than exosomes. However, there remains a substantial need to focus on systematic compatibility, efficiency, and biosafety issues. Despite a great deal of effort have been done, there are no clinically available exosomes-related products for the diagnosis and treatment of RA. Exosomal ncRNAs hold profound promise as diagnostic and therapeutic biomarkers, and we should remain optimistic to achieve health-beneficial fusion. In conclusion, this review may have notable implications for laboratory and clinical research to develop promising diagnostic and therapeutic biomarkers as well as target-based innovative biological agents, making RA no longer untreatable.

Abbreviations

Rheumatoid arthritis (RA); non-coding RNAs (ncRNAs); Extracellular vesicles (EVs); rheumatoid factors (RF); antibodies against cyclic citrullinated peptides (ACPA); disease-modifying anti-rheumatic drugs (DMARDs); mesenchymal stem cells (MSCs); osteoarthritis (OA); extracellular matrix (ECM); fibroblast-like synoviocytes (FLSs); RA synovial fibroblasts (RASFs); Bone marrow MSCs (BMSCs); Human umbilical cord MSCs (hUCMSCs); Gingival MSCs (GMSCs); Adipose-derived stem cells (ADSCs); Granulocytic myeloid-derived suppressor cells (G-MDSCs); collagen-induced arthritis (CIA); polymorphonuclear neutrophil-derived EVs (PMN-EVs).

Acknowledgments

This study was supported by funding from the National Natural Science Foundation of China (Grant No.82104298).

Author Contributions

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

Disclosure

The authors declare that they have no known competing financial interests or personal relationships with other people or organizations that could have influenced the work reported in this paper.

References

1. Klareskog L, Catrina AI, Paget S. Rheumatoid arthritis. *Lancet*. 2009;373(9664):659–672. doi:10.1016/S0140-6736(09)60008-8
2. Smolen JS, Aletaha D, McInnes IB. Rheumatoid arthritis. *Lancet*. 2016;388(10055):2023–2038. doi:10.1016/S0140-6736(16)30173-8
3. Smolen JS, Aletaha D, Barton A, et al. Rheumatoid arthritis. *Nature Reviews Disease Primers*. 2018;4(1):18001. doi:10.1038/nrdp.2018.1
4. Aletaha D, Smolen JS. Diagnosis and management of rheumatoid arthritis: a review. *JAMA*. 2018;320(13):1360–1372. doi:10.1001/jama.2018.13103
5. Radu A-F, Bungau SG. Management of rheumatoid arthritis: an overview. *Cells*. 2021;10(11):2857. doi:10.3390/cells10112857
6. McInnes IB, Schett G. The pathogenesis of rheumatoid arthritis. *N Engl J Med*. 2011;365(23):2205–2219. doi:10.1056/NEJMra1004965
7. Zhang W, Song M, Qu J, Liu G-H. Epigenetic modifications in cardiovascular aging and diseases. *Circulation Resea*. 2018;123(7):773–786. doi:10.1161/CIRCRESAHA.118.312497
8. Xu Y-X, Pu S-D, Li X, et al. Exosomal ncRNAs: novel therapeutic target and biomarker for diabetic complications. *Pharmacol Res*. 2022;178:106135. doi:10.1016/j.phrs.2022.106135
9. Miao H-B, Wang F, Lin S, Chen Z. Update on the role of extracellular vesicles in rheumatoid arthritis. *Expert Revi Molecr Med*. 2022;24:e12. doi:10.1017/erm.2021.33
10. Miao C, Wang X, Zhou W, Huang J. The emerging roles of exosomes in autoimmune diseases, with special emphasis on microRNAs in exosomes. *Pharmacol Res*. 2021;169:105680. doi:10.1016/j.phrs.2021.105680

11. Xue L, Wang B, Li X, et al. Comprehensive analysis of serum exosome-derived lncRNAs and mRNAs from patients with rheumatoid arthritis. *Arthritis Res Therapy*. 2023;25(1):201. doi:10.1186/s13075-023-03174-9
12. Shuai Z-Q, Wang Z-X, Ren J-L, Yang X-K, Xu B. Differential expressions and potential clinical values of lncRNAs in the plasma exosomes of rheumatoid arthritis. *Int Immunopharm*. 2024;128:111511. doi:10.1016/j.intimp.2024.111511
13. Singh A, Patro PS, Aggarwal A. MicroRNA-132, miR-146a, and miR-155 as potential biomarkers of methotrexate response in patients with rheumatoid arthritis. *Clin Rheumatol*. 2019;38:877–884. doi:10.1007/s10067-018-4380-z
14. Hruskova V, Jandova R, Vernerova L, et al. MicroRNA-125b: association with disease activity and the treatment response of patients with early rheumatoid arthritis. *Arthritis Res Therap*. 2016;18:1–8. doi:10.1186/s13075-016-1023-0
15. Mirzaei R, Zamani F, Hajibaba M, et al. The pathogenic, therapeutic and diagnostic role of exosomal microRNA in the autoimmune diseases. *J Neuroimmun*. 2021;358:577640. doi:10.1016/j.jneuroim.2021.577640
16. Hejrati A, Hasani B, Esmaili M, Bashash D, Tavakolinia N, Zafari P. Role of exosome in autoimmunity, with a particular emphasis on rheumatoid arthritis. *Inte J Rheumatic Dise*. 2021;24(2):159–169. doi:10.1111/1756-185X.14021
17. Wolf P. The nature and significance of platelet products in human plasma. *Br J Haematol*. 1967;13(3):269–288. doi:10.1111/j.1365-2141.1967.tb08741.x
18. Trams EG, Lauter CJ, Salem JN, Heine U. Exfoliation of membrane ecto-enzymes in the form of micro-vesicles. *Biochimica et Biophysica Acta (BBA)-Biomembranes*. 1981;645(1):63–70. doi:10.1016/0005-2736(81)90512-5
19. Pan B-T, Johnstone RM. Fate of the transferrin receptor during maturation of sheep reticulocytes in vitro: selective externalization of the receptor. *Cell*. 1983;33(3):967–978. doi:10.1016/0092-8674(83)90040-5
20. Stegmayr B, Brody I, Ronquist G. A biochemical and ultrastructural study on the endogenous protein kinase activity of secretory granule membranes of prostatic origin in human seminal plasma. *J Ultrastruct Res*. 1982;78(2):206–214. doi:10.1016/S0022-5320(82)80024-5
21. Harding C, Heuser J, Stahl P. Receptor-mediated endocytosis of transferrin and recycling of the transferrin receptor in rat reticulocytes. *J Cell Biol*. 1983;97(2):329–339. doi:10.1083/jcb.97.2.329
22. Raposo G, Nijman HW, Stoorvogel W, et al. B lymphocytes secrete antigen-presenting vesicles. *J Exp Med*. 1996;183(3):1161–1172. doi:10.1084/jem.183.3.1161
23. Zitvogel LA, Regnault A, Lozier J, et al. Eradication of established murine tumors using a novel cell-free vaccine: dendritic cell derived exosomes. *Nature Med*. 1998;4(5):594–600. doi:10.1038/nm0598-594
24. Valadi H, Ekström K, Bossios A, Sjöstrand M, Lee JJ, Lötvall JO. 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
25. Zomer A, Maynard C, Verweij FJ, et al. In vivo imaging reveals extracellular vesicle-mediated phenocopying of metastatic behavior. *Cell*. 2015;161(5):1046–1057. doi:10.1016/j.cell.2015.04.042
26. Van G, Niel G, d'Angelo G. Raposo, Shedding light on the cell biology of extracellular vesicles. *Nat Rev Mol Cell Biol*. 2018;19(4):213–228. doi:10.1038/nrm.2017.125
27. Cocucci E, Meldolesi J. Ectosomes and exosomes: shedding the confusion between extracellular vesicles. *Trends Cell Biol*. 2015;25(6):364–372. doi:10.1016/j.tcb.2015.01.004
28. Kalluri R, LeBleu VS. The biology, function, and biomedical applications of exosomes. *Science*. 2020;367(6478):eaau6977. doi:10.1126/science.aau6977
29. Xu M, Feng T, Liu B, et al. Engineered exosomes: desirable target-tracking characteristics for cerebrovascular and neurodegenerative disease therapies. *Theranostics*. 2021;11(18):8926. doi:10.7150/thno.62330
30. Elliott RO, He M. Unlocking the power of exosomes for crossing biological barriers in drug delivery. *Pharmaceutics*. 2021;13(1):122. doi:10.3390/pharmaceutics13010122
31. Alvarez-Erviti L, Seow Y, Yin H, Betts C, Lakhal S, Wood MJ. Delivery of siRNA to the mouse brain by systemic injection of targeted exosomes. *Nature Biotechnol*. 2011;29(4):341–345. doi:10.1038/nbt.1807
32. Wang X, Zhao X, Zhong Y, Shen J, An W. Biomimetic exosomes: a new generation of drug delivery system. *Front Bioeng Biotech*. 2022;10:865682. doi:10.3389/fbioe.2022.865682
33. Yao X, Mao Y, Wu D, et al. Exosomal circ_0030167 derived from BM-MSCs inhibits the invasion, migration, proliferation and stemness of pancreatic cancer cells by sponging miR-338-5p and targeting the Wif1/Wnt8/β-catenin axis. *Cancer Lett*. 2021;512:38–50. doi:10.1016/j.canlet.2021.04.030
34. Michael BNR, Kommoju V, Kavadichanda Ganapathy C, Negi VS. Characterization of cell-derived microparticles in synovial fluid and plasma of patients with rheumatoid arthritis. *Rheumatology Int*. 2019;39(8):1377–1387. doi:10.1007/s00296-019-04337-1
35. Song JE, Kim JS, Shin JH, et al. Role of synovial exosomes in osteoclast differentiation in inflammatory arthritis. *Cells*. 2021;10(1):120. doi:10.3390/cells10010120
36. Schioppo T, Ubiali T, Ingegnoli F, et al. The role of extracellular vesicles in rheumatoid arthritis: a systematic review. *Clin Rheumatol*. 2021;40(9):3481–3497. doi:10.1007/s10067-021-05614-w
37. Distler JH, Jüngel A, Huber LC, et al., The induction of matrix metalloproteinase and cytokine expression in synovial fibroblasts stimulated with immune cell microparticles, Proceedings of the National Academy of Sciences. 102(8):2892–2897.
38. Headland SE, Jones HR, Norling LV, et al. Neutrophil-derived microvesicles enter cartilage and protect the joint in inflammatory arthritis. *Sci trans med*. 2015;7(315):315ra190–315ra190. doi:10.1126/scitranslmed.aac5608
39. Qin Q, Song R, Du P, Gao C, Yao Q, Zhang J-A. Systemic proteomic analysis reveals distinct exosomal protein profiles in rheumatoid arthritis. *J Immunology Rese*. 2021;2021:1–11. doi:10.1155/2021/9421720
40. Burbano C, Rojas M, Muñoz-Vahos C, et al. Extracellular vesicles are associated with the systemic inflammation of patients with seropositive rheumatoid arthritis. *Sci Rep*. 2018;8(1):17917. doi:10.1038/s41598-018-36335-x
41. Burbano C, Villar-Vesga J, Vásquez G, Muñoz-Vahos C, Rojas M, Castaño D. Proinflammatory differentiation of macrophages through microparticles that form immune complexes leads to T-and B-cell activation in systemic autoimmune diseases. *Front Immunol*. 2058;10(2019).
42. 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

43. Withrow J, Murphy C, Liu Y, Hunter M, Fulzele S, Hamrick MW. Extracellular vesicles in the pathogenesis of rheumatoid arthritis and osteoarthritis. *Arthritis Res Therap*. 2016;18(1):1–12. doi:10.1186/s13075-016-1178-8
44. Marton N, Kovács OT, Baricza E, et al. Extracellular vesicles regulate the human osteoclastogenesis: divergent roles in discrete inflammatory arthropathies. *Cell Mol Life Sci* 2017;74:3599–3611. doi:10.1007/s00018-017-2535-8
45. Frank-Bertoncelj M, Pisetsky DS, Kolling C, et al. TLR3 ligand poly (I: c) exerts distinct actions in synovial fibroblasts when delivered by extracellular vesicles. *Front Immunol*. 2018;9:28. doi:10.3389/fimmu.2018.00028
46. Manček-Keber M, Frank-Bertoncelj M, Hafner-Bratkovič I, et al. Toll-like receptor 4 senses oxidative stress mediated by the oxidation of phospholipids in extracellular vesicles. *Sci Signaling*. 2015;8(381):ra60–ra60. doi:10.1126/scisignal.2005860
47. Lin Z, Li W, Wang Y, et al. SMSCs-derived sEV overexpressing miR-433-3p inhibits angiogenesis induced by sEV released from synoviocytes under triggering of ferroptosis. *Int Immunopharm*. 2023;116:109875. doi:10.1016/j.intimp.2023.109875
48. Li SR, Man QW, Gao X, et al. Tissue-derived extracellular vesicles in cancers and non-cancer diseases: present and future. *J Extracell Vesicles*. 2021;10(14):e12175. doi:10.1002/jev2.12175
49. Palanisamy CP, Pei J, Alugoju P, et al. New strategies of neurodegenerative disease treatment with extracellular vesicles (EVs) derived from mesenchymal stem cells (MSCs. *Theranostics*. 2023;13(12):4138. doi:10.7150/thno.83066
50. Liu H, Li R, Liu T, Yang L, Yin G, Xie Q. Immunomodulatory effects of mesenchymal stem cells and mesenchymal stem cell-derived extracellular vesicles in rheumatoid arthritis. *Front Immunol*. 1912;11(2020).
51. Ragni E, Palombella S, Lopa S, et al. Innovative visualization and quantification of extracellular vesicles interaction with and incorporation in target cells in 3D microenvironments. *Cells*. 2020;9(5):1180. doi:10.3390/cells9051180
52. Casado JG, Blázquez R, Vela FJ, Álvarez V, Tarazona R, Sánchez-Margallo FM. Mesenchymal stem cell-derived exosomes: immunomodulatory evaluation in an antigen-induced synovitis porcine model. *Front Veterina Scien*. 2017;4:39. doi:10.3389/fvets.2017.00039
53. 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. doi:10.7150/thno.21072
54. Xu K, Ma D, Zhang G, et al. Human umbilical cord mesenchymal stem cell-derived small extracellular vesicles ameliorate collagen-induced arthritis via immunomodulatory T lymphocytes. *Mol Immunol*. 2021;135:36–44. doi:10.1016/j.molimm.2021.04.001
55. Ma D, Xu K, Zhang G, et al. Immunomodulatory effect of human umbilical cord mesenchymal stem cells on T lymphocytes in rheumatoid arthritis. *Int Immunopharmacol*. 2019;74:105687. doi:10.1016/j.intimp.2019.105687
56. Wang R, Ji Q, Meng C, et al. Role of gingival mesenchymal stem cell exosomes in macrophage polarization under inflammatory conditions. *Int Immunopharmacol*. 2020;81:106030. doi:10.1016/j.intimp.2019.106030
57. Gonzalez-Rey E, Gonzalez MA, Varela N, et al. Human adipose-derived mesenchymal stem cells reduce inflammatory and T cell responses and induce regulatory T cells in vitro in rheumatoid arthritis. *Ann Rheumatic Dis*. 2010;69(01):241–248. doi:10.1136/ard.2008.101881
58. Li Q, Yu H, Sun M, et al. The tissue origin effect of extracellular vesicles on cartilage and bone regeneration. *Acta Biomater*. 2021;125:253–266. doi:10.1016/j.actbio.2021.02.039
59. Zhang Y, Wang Z, Shi B, et al. Effect of gingival mesenchymal stem cell-derived exosomes on inflammatory macrophages in a high-lipid microenvironment. *Int Immunopharmacol*. 2021;94:107455. doi:10.1016/j.intimp.2021.107455
60. Wu X, Zhu D, Tian J, et al. Granulocytic myeloid-derived suppressor cell exosomal prostaglandin E2 Ameliorates Collagen-Induced Arthritis by Enhancing IL-10+ B Cells. *Front Immunol*. 2020;11:588500. doi:10.3389/fimmu.2020.588500
61. Zhu D, Tian J, Wu X, et al. G-MDSC-derived exosomes attenuate collagen-induced arthritis by impairing Th1 and Th17 cell responses. *Biochimica Et Biophysica Acta (BBA)-Molecular Basis Disease*. 2019;1865(12):165540. doi:10.1016/j.bbadis.2019.165540
62. Zhang L, Qin Z, Sun H, et al. Nanoenzyme engineered neutrophil-derived exosomes attenuate joint injury in advanced rheumatoid arthritis via regulating inflammatory environment. *Bioact Mate*. 2022;18:1–14. doi:10.1016/j.bioactmat.2022.02.017
63. You DG, Lim GT, Kwon S, et al. Metabolically engineered stem cell–derived exosomes to regulate macrophage heterogeneity in rheumatoid arthritis. *Sci Adv*. 2021;7(23):eabe0083. doi:10.1126/sciadv.abe0083
64. Patop IL, Wüst S, Kadener S. Past, present, and future of circ RNA s. *EMBO J*. 2019;38(16):e100836. doi:10.15252/embj.2018100836
65. Kristensen LS, Andersen MS, Stagsted LV, Ebbesen KK, Hansen TB, Kjems J. The biogenesis, biology and characterization of circular RNAs. *Nat Rev Genet*. 2019;20(11):675–691. doi:10.1038/s41576-019-0158-7
66. 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. doi:10.2147/JIR.S336099
67. 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 Nanomed*;2021. 7977–7994. doi:10.2147/IJN.S333465
68. Li G, Fang Y, Xu N, Ding Y, Liu D. Fibroblast-like synoviocytes-derived exosomal circFTO deteriorates rheumatoid arthritis by enhancing N6-methyladenosine modification of SOX9 in chondrocytes. *Arthritis Res Therapy*. 2024;26(1):56. doi:10.1186/s13075-024-03290-0
69. Song J, Kim D, Han J, Kim Y, Lee M, Jin E-J. PBMC and exosome-derived Hotair is a critical regulator and potent marker for rheumatoid arthritis. *Clin Exp Med*. 2015;15:121–126. doi:10.1007/s10238-013-0271-4
70. 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 Develop Biol*. 2020;8:551681. doi:10.3389/fcell.2020.551681
71. Liu R, Jiang C, Li J, et al. Serum-derived exosomes containing NEAT1 promote the occurrence of rheumatoid arthritis through regulation of miR-144-3p/ROCK2 axis. *Therapeutic Advan Chronic Disease*. 2021;12:2040622321991705. doi:10.1177/2040622321991705
72. 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
73. 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

74. 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 Orthopaedic Surg Res*. 2021;16(1):1–14. doi:10.1186/s13018-021-02248-1
75. Sun S, Liang L, Tian R, et al. LncRNA expression profiling in exosomes derived from synovial fluid of patients with rheumatoid arthritis. *Int Immunopharm*. 2024;130:111735. doi:10.1016/j.intimp.2024.111735
76. Derrien T, Johnson R, Bussotti G, et al. The GENCODE v7 catalog of human long noncoding RNAs: analysis of their gene structure, evolution, and expression. *Genome Res*. 2012;22(9):1775–1789. doi:10.1101/gr.132159.111
77. Kopp F, Mendell JT. Functional classification and experimental dissection of long noncoding RNAs. *Cell*. 2018;172(3):393–407. doi:10.1016/j.cell.2018.01.011
78. 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
79. Liu Y, Lin L, Zou R, Wen C, Wang Z, Lin F. 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
80. Saferding V, Puchner A, Goncalves-Alves E, et al. MicroRNA-146a governs fibroblast activation and joint pathology in arthritis. *J Autoimmun*. 2017;82:74–84. doi:10.1016/j.jaut.2017.05.006
81. Lee W, Kato M, Sugawara E, et al. Optineurin in Synovial Fibroblasts Plays a Protective Role Against Joint Destructions in Rheumatoid Arthritis. *Arthritis Rheumatol*. 2020;72(9):1493–1504. doi:10.1002/art.41290
82. Bi X, Guo XH, Mo BY, et al. LncRNA PICSAR promotes cell proliferation, migration and invasion of fibroblast-like synoviocytes by sponging miRNA-4701-5p in rheumatoid arthritis. *EBioMedicine*. 2019;50:408–420. doi:10.1016/j.ebiom.2019.11.024
83. Saliminejad K, Khorram Khorshid HR, Soleymani Fard S, Ghaffari SH. An overview of microRNAs: biology, functions, therapeutics, and analysis methods. *J Cell Physiol*. 2019;234(5):5451–5465. doi:10.1002/jcp.27486
84. Du S, Ling H, Guo Z, Cao Q, Song C. Roles of exosomal miRNA in vascular aging. *Pharmacol Res*. 2021;165:105278. doi:10.1016/j.phrs.2020.105278
85. Wu L-F, Zhang Q, Mo X-B, et al. Identification of novel rheumatoid arthritis-associated MiRNA-204-5p from plasma exosomes. *Exp Mol Med*. 2022;54(3):334–345. doi:10.1038/s12276-022-00751-x
86. Xu D, Song M, Chai C, et al. Exosome-encapsulated miR-6089 regulates inflammatory response via targeting TLR4. *J Cell Physiol*. 2019;234(2):1502–1511. doi:10.1002/jcp.27014
87. Lim M-K, Yoo J, Sheen D-H, Ihm C, Lee SK, Kim SA. Serum exosomal miRNA-1915-3p is correlated with disease activity of Korean rheumatoid arthritis. *in vivo*. 2020;34(5):2941–2945. doi:10.21873/invivo.12124
88. Rodríguez-Muguruza S, Altuna-Coy A, Castro-Oreiro S, Poveda-Elices MJ, Fontova-Garrofé R, Chacón MR. 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
89. Wang L, Wang C, Jia X, et al. Circulating exosomal miR-17 inhibits the induction of regulatory T cells via suppressing TGFBR II expression in rheumatoid arthritis. *Cell Physiol Biochem*. 2018;50(5):1754–1763. doi:10.1159/000494793
90. Wang Y, Zheng F, Gao G, et al. MiR-548a-3p regulates inflammatory response via TLR4/NF-κB signaling pathway in rheumatoid arthritis. *J Cell Biochem*. 2019;120(2):1133–1140. doi:10.1002/jcb.26659
91. 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 Immunopharm*. 2023;120:110286. doi:10.1016/j.intimp.2023.110286
92. Gong J, Zhang X, Khan A, et al. Identification of serum exosomal miRNA biomarkers for diagnosis of Rheumatoid arthritis. *Int Immunopharm*. 2024;129:111604. doi:10.1016/j.intimp.2024.111604
93. Takamura Y, Aoki W, Satomura A, Shibasaki S, Ueda M, Zheng Y. Small RNAs detected in exosomes derived from the MH7A synovial fibroblast cell line with TNF-α stimulation. *PLoS One*. 2018;13(8):e0201851. doi:10.1371/journal.pone.0201851
94. Ding Y, Wang L, Wu H, Zhao Q, Wu S. Exosomes derived from synovial fibroblasts under hypoxia aggravate rheumatoid arthritis by regulating Treg/Th17 balance. *Exp Biol Med*. 2020;245(14):1177–1186. doi:10.1177/1535370220934736
95. 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*. 2020;98(3):409–423. doi:10.1007/s00109-020-01882-2
96. Maeda Y, Farina NH, Matzelle MM, Fanning PJ, Lian JB, Gravallese EM. Synovium-derived microRNAs regulate bone pathways in rheumatoid arthritis. *J Bone Miner Res*. 2017;32(3):461–472. doi:10.1002/jbmr.3005
97. Hegewald AB, Breitwieser K, Ottinger SM, et al. Extracellular miR-574-5p induces osteoclast differentiation via TLR 7/8 in rheumatoid arthritis. *Front Immunol*. 2020;11:585282. doi:10.3389/fimmu.2020.585282
98. Chen M, Li M, 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
99. Kim S, Chen Z, Essani A, et al. Identification of a Novel Toll-like Receptor 7 Endogenous Ligand in Rheumatoid Arthritis Synovial Fluid That Can Provoke Arthritic Joint Inflammation. *Arthritis Rheumatol*. 2016;68(5):1099–1110. doi:10.1002/art.39544
100. 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
101. Zhang B, Gu J, Wang Y, Guo L, Xie J, Yang M. TNF-α stimulated exosome derived from fibroblast-like synoviocytes isolated from rheumatoid arthritis patients promotes HUVEC migration, invasion and angiogenesis by targeting the miR-200a-3p/KLF6/VEGFA axis. *Autoimmunity*. 2023;56(1):2282939. doi:10.1080/08916934.2023.2282939
102. Xin Y, Yang Z, Fei X, et al. Plasma exosomal mir-92a are involved in the occurrence and development of bone destruction in ra patients by inhibiting apoptosis of fibroblast-like synoviocytes. *Ann Rheuma Dis*. 2018;THU0059.
103. Zheng J, Zhu L, In II, Chen Y, Jia N, Zhu W. Bone marrow-derived mesenchymal stem cells-secreted exosomal microRNA-192-5p delays inflammatory response in rheumatoid arthritis. *Int Immunopharmacol*. 2020;78:105985. doi:10.1016/j.intimp.2019.105985
104. Wu H, Zhou X, Wang X, et al. Gu, miR-34a in extracellular vesicles from bone marrow mesenchymal stem cells reduces rheumatoid arthritis inflammation via the cyclin I/ATM/ATR/p53 axis. *J Cell & Mol Med*. 2021;25(4):1896–1910. doi:10.1111/jcmm.15857

105. Ma W, Tang F, Xiao L, et al. Zhou, miR-205-5p in exosomes divided from chondrogenic mesenchymal stem cells alleviated rheumatoid arthritis via regulating MDM2 in fibroblast-like synoviocytes. *J Musculoskeletal & Neuronal Inter*. 2022;22(1):132.
106. Huang Y, Chen L, Chen D, Fan P, Yu H. 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):1–14. doi:10.1186/s10020-022-00451-2
107. Chen Z, Wang H, Xia Y, Yan F, Lu Y. 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
108. Meng H-Y, Chen L-Q, Chen L-H. The inhibition by human MSCs-derived miRNA-124a overexpression exosomes in the proliferation and migration of rheumatoid arthritis-related fibroblast-like synoviocyte cell. *BMC Musculoskeletal Disorders*. 2020;21:1–10. doi:10.1186/s12891-020-3159-y
109. 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
110. Li G-Q, Fang Y-X, Liu Y, et al. MicroRNA-21 from bone marrow mesenchymal stem cell-derived extracellular vesicles targets TET1 to suppress KLF4 and alleviate rheumatoid arthritis. *Therapeutic Advances in Chronic Disease*. 2021;12:20406223211007369. doi:10.1177/20406223211007369
111. Meng Q, Qiu B. Exosomal microRNA-320a derived from mesenchymal stem cells regulates rheumatoid arthritis fibroblast-like synoviocyte activation by suppressing CXCL9 expression. *Front Physiol*. 2020;11:441. doi:10.3389/fphys.2020.00441
112. Tavasolian F, Hosseini AZ, Soudi S, et al. Naderi, miRNA-146a improves immunomodulatory effects of MSC-derived exosomes in rheumatoid arthritis. *Current Gene Therapy*. 2020;20(4):297–312. doi:10.2174/1566523220666200916120708
113. Li N, Chen Z, Feng W, et al. Triptolide improves chondrocyte proliferation and secretion via down-regulation of miR-221 in synovial cell exosomes. *Phytomedicine*. 2022;107:154479. doi:10.1016/j.phymed.2022.154479
114. Zhang Y, Jiao Z, Wang S. Bone Marrow Mesenchymal Stem Cells Release miR-378a-5p-Carried Extracellular Vesicles to Alleviate Rheumatoid Arthritis. *Journal of Innate Immunity*. 2023;15(1):893–910. doi:10.1159/000534830
115. Chen J, Shi X, Deng Y, et al. Xiong, miRNA-148a–containing GMSC-derived EVs modulate Treg/Th17 balance via IKKB/NF-κB pathway and treat a rheumatoid arthritis model. *JCI Insight*. 2024;9(10). doi:10.1172/jci.insight.177841
116. Liang Y, Duan L, Lu J, Xia J. Engineering exosomes for targeted drug delivery. *Theranostics*. 2021;11(7):3183. doi:10.7150/thno.52570
117. Zhou R, Chen Y, Li S, et al. TRPM7 channel inhibition attenuates rheumatoid arthritis articular chondrocyte ferroptosis by suppression of the PKCα-NOX4 axis. *Redox Biol*. 2022;55:102411. doi:10.1016/j.redox.2022.102411
118. Kurowska-Stolarska M, Alivernini S. Synovial tissue macrophages in joint homeostasis, rheumatoid arthritis and disease remission. *Nat Rev Rheumatol*. 2022;18(7):384–397. doi:10.1038/s41584-022-00790-8