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REVIEW

Emerging Role and Mechanism of Mesenchymal Stem Cells-Derived Extracellular Vesicles in Rheumatic Disease

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Abstract: Mesenchymal stem cells (MSCs) are pluripotent stem cells derived from mesoderm. Through cell-to-cell contact or paracrine effects, they carry out biological tasks like immunomodulatory, anti-inflammatory, regeneration, and repair. Extracellular vesicles (EVs) are the primary mechanism for the paracrine regulation of MSCs. They deliver proteins, nucleic acids, lipids, and other active compounds to various tissues and organs, thus facilitating intercellular communication. Rheumatic diseases may be treated using MSCs and MSC-derived EVs (MSC-EVs) due to their immunomodulatory capabilities, according to mounting data. Since MSC-EVs have low immunogenicity, high stability, and similar biological effects as to MSCs themselves, they are advantageous over cell therapy for potential therapeutic applications in rheumatoid arthritis, systemic erythematosus lupus, systemic sclerosis, Sjogren's syndrome, and other rheumatoid diseases. This review integrates recent advances in the characteristics, functions, and potential molecular mechanisms of MSC-EVs in rheumatic diseases and provides a new understanding of the pathogenesis of rheumatic diseases and MSC-EV-based treatment strategies.

Keywords: mesenchymal stem cells, extracellular vesicles, exosome, immunomodulation, rheumatic disease

Introduction

Rheumatic diseases are refractory conditions that affect multiple systems and organs and are primarily brought on by autoimmune responses.[1] Abnormal activation of immune cells due to acute or chronic infection results in abundant immune reaction, large amounts of autoantibodies, deposition of immune complexes, and inflammatory response, which thus causes damages to specific tissues and organs, leading to arthralgia, skin lesions, myalgia, dry mouth, dry eyes, hair loss, and other clinical symptoms. The most prevalent conditions are rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), systemic sclerosis (SSc), Sjogren's syndrome (SS), and osteoarthritis (OA). Currently, hormones, antirheumatic drugs, and biological agents are the principal medications to treat rheumatic disorders.[2] However, not all patients respond well to those drug therapies, and some patients still can not achieve disease remission after standardized treatments. Furthermore, long-term use of antirheumatic drugs often leads to serious side effects in several patients with rheumatic disorders. Therefore, one problem that needs to be resolved is identifying novel therapeutic targets for rheumatic disease.

Mesenchymal Stem Cells (MSCs)

Stem cells have proven beneficial in recent times for autoimmune illnesses like SLE, RA, and SSc.[3–5] MSCs widely exist in the bone marrow, umbilical cords, peripheral blood, fatty tissue, and other tissues. They are adult stem cells with multidirectional

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differentiation potentials. MSCs serve as a promising stem cell-based therapeutic choice and possess properties of regeneration, repair, anti-inflammation, and immunomodulation. However, MSC treatment, as a live cell therapy, inevitably has safety concerns of tumorigenicity and transplant rejection. Accumulated evidence has revealed that MSC-derived extracellular vesicles (MSC-EVs) also perform strong biological functions similar to MSCs by transferring active molecules to the corresponding organs and tissues, such as proteins, nucleic acids, and lipids. More importantly, MSC-EVs exert biological effects with excellent biocompatibility and stability in rheumatic disorders, such as exosomes, which are the most common particles with diameters less than 200 nm in size. In our previously published review, the role of MSCs and MSC-EVs in SLE has been summarized.[6] In the current paper, an updated review of MSCs and MSC-EVs in regulating innate and adaptive immunity rheumatoid arthritis has been performed, primarily including SLE, SS, RA, and SSc. This review will be useful to explore new therapeutic strategies for rheumatic diseases based on MSC-EVs.

Biological Characterization of MSC and MSC-EVs

MSCs can differentiate into various cells, including osteoblasts,[7] fat cells,[8] and chondrocytes.[9] MSCs display low immunogenicity, multidirectional differentiation, self-renewal, and immunomodulatory characteristics. Thus, MSCs are star cells for regeneration medicine suggested by several studies on preclinical research and Phase I/II clinical trials.[10–12] MSCs express surface markers such as CD105, CD73 and CD90, while lacking expression of CD45, CD34, CD11b, CD19, and HLA-DR.[13] Multiple studies have confirmed that MSCs can influence monocytes/macrophages, T cells, and B cells by producing bioactive factors in autoimmune and inflammatory diseases.[14–16]

In recent years, many studies have reported that many bioactive factors are encapsulated and delivered by MSC-EVs, which subsequently participate in the intercellular communications between MSCs and the recipient cells, including Immune and histological cells (Figure 1). EVs are heterogeneous particles with lipid bilayers that can be secreted by all cell types and mediate intercellular communication. EVs can transport lipids, proteins, and nucleic acids to target cells.[17] EVs are categorized into exosomes, microvesicles, and apoptotic vesicles by size. These vesicles play a crucial role in intracellular signaling transduction in MSCs. Apoptotic vesicles are the largest vesicles with a diameter of up to 5000 nm, forming during the late stage of apoptosis through direct budding of the membrane.[18] Microvesicles, with the diameter ranging from 100 to 1000 nm, are generated by the budding and shedding of the cell membrane following fusion with the cell membrane.[19] Exosomes are known as the smallest particles, ranging from 30 and 150 nm in size, which are formed when the cell membrane is endocytosed (Figure 1).[20] Exosomes are one of the most prevalent EVs among them. They have a diameter of 30–150nm, specifically expressing phenotypic markers like CD9, CD63, and CD81. Exosomes confer biological effects by delivering functional molecules to specific sites. Via EVs, T cells, B cells, and MSCs can carry out biological functions by secreting paracrine substances (Figure 2). MSC-EVs are secreted from inside the cell to the outside and like MSCs, have functions of immune regulation, tissue regeneration, and wound healing. EVs derived from MSCs contain a substantial quantity of miRNAs, which play significant roles in various physiological and pathological processes (Figure 2).

MSC-EVs exhibit biological activities similar to those of MSCs, with much lower immunogenicity and higher stability. Although most research has demonstrated that MSC has anti-cancer effects, Gloria Bonuccelli et al have found that MSC makes osteosarcoma cells more aggressive.[21] Furthermore, two patients receiving MSC therapy for renal illness experienced thrombosis.[22] Pulmonary embolism after treatment with MSC in both in vivo and clinical trials.[23,24] For patients, these MSC side effects might be quite harmful. In terms of safety, MSC-EV is not affected by these and can be used as a good treatment.[25] Patients with grade III–IV CKD treated with cell-free cord-blood mesenchymal stem cells derived extracellular vesicles (CF-CB-MSCs-EVs) have shown improvements in their overall renal function, and there are no known concerns related to MSC therapy, such as tumorigenicity or pulmonary embolism (Table 1).[26] In a Phase 2a clinical trial study (NCT04276987) conducted in Wuhan, China, seven patients with severe COVID-19 pneumonia who received nebulized inhalation of human adipose-derived MSCs-Exosomes (haMSC-Exos) showed varying degrees of regression of lung lesions and significant relief of symptoms (Table 1).[27] In a different clinical study, a patient treated with MSC-Exo for Graft-versus-Host disease demonstrated a reduction in inflammatory factors in the peripheral blood and an improvement in clinical symptoms of GvHD (Table 1).[28] Although the patient died of pneumonia after 7 months

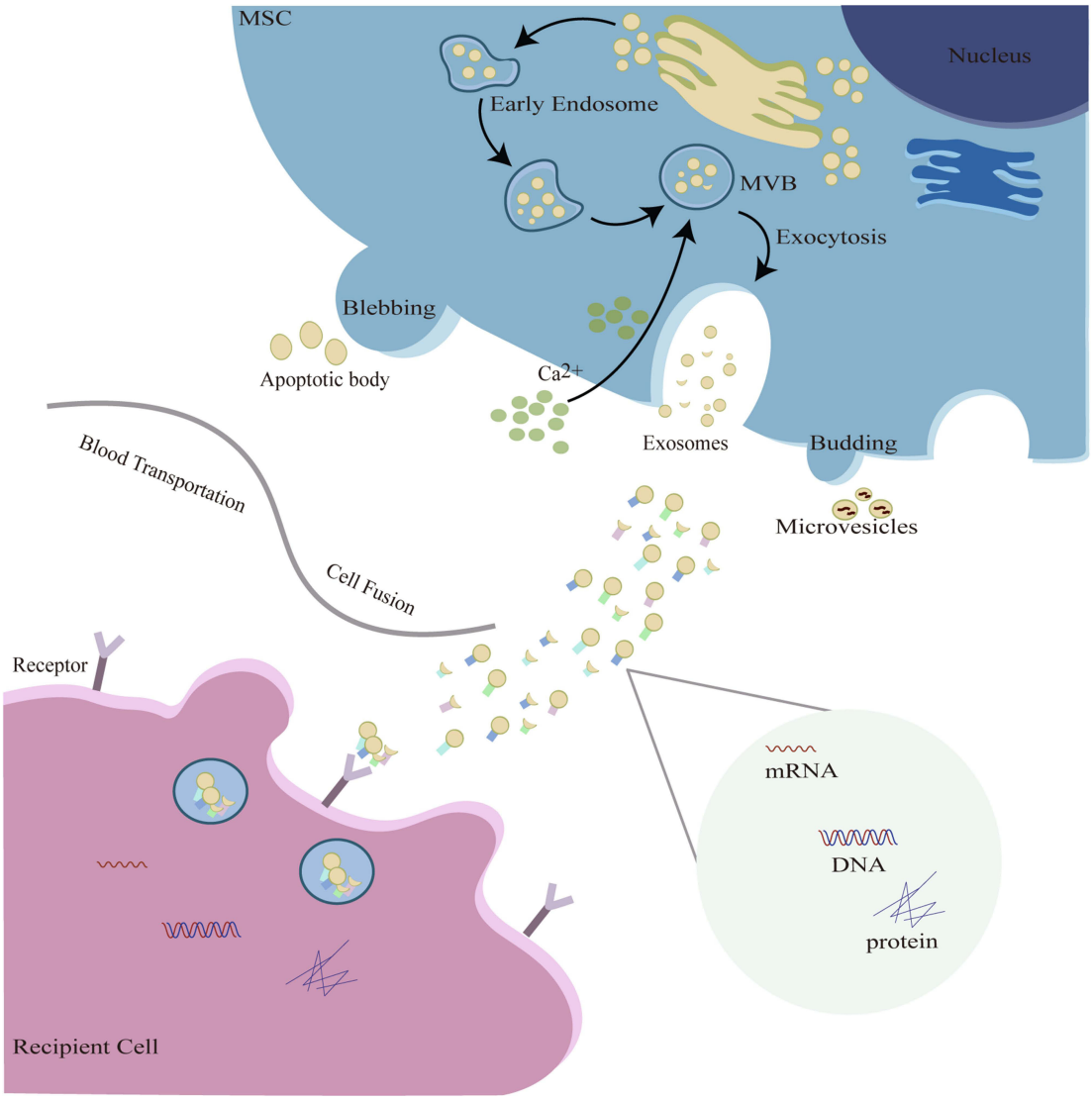

Figure 1 The formation of EVs derived from MSCs. Inside MSCs, the membrane invaginations form early endosomes, which further mature into multivesicular bodies (MVB). MVBs fuse with the cell membrane and release their internal intracavicular vesicles outside the cell to form exosomes. As an important medium of intercellular communication, exosomes carry and deliver a variety of bioactive molecules, such as proteins, DNA, mRNA, etc., to regulate the function of recipient cells by direct contaction or transporting these bioactive molecules.

of exosomes, the improvement in these symptoms still provides evidence for effective treatment of GvHD.[28] Thus, MSC-EVs are promising cell-free nanoparticles for future biotherapeutics.

Regulation of Innate Immunity by MSC-EVs

Regulation of Macrophages by MSC-EVs

Macrophages are critical cells involved in innate immunity, which are responsible for removing necrotic debris and pathogens from the damaged tissues. Macrophages are highly plastic and can be divided into M1 proinflammatory cells and M2 anti-inflammatory cells. MSC-EVs can help convert M1 to M2, according to numerous research (Table 2 and Figure 2). After receiving MSC-Exos, mice's colitis is lessened because their M2-like substance is expressed, while their M1-like substance is less.[30] Exosomes derived from human umbilical cord MSCs (hUMSC-Exos) have been suggested to alleviate steroid-resistant asthma by inhibiting M1 but promoting M2 polarization via suppressing tumor necrosis factor receptor-related factor 1.[31] Also, MSC-EV reduced salpingitis by shaping macrophage from M1 to M2.[32] Furthermore, some bioactive molecules encapsulated in MSC-EVs can also regulate macrophage functions and phenotypes, such as

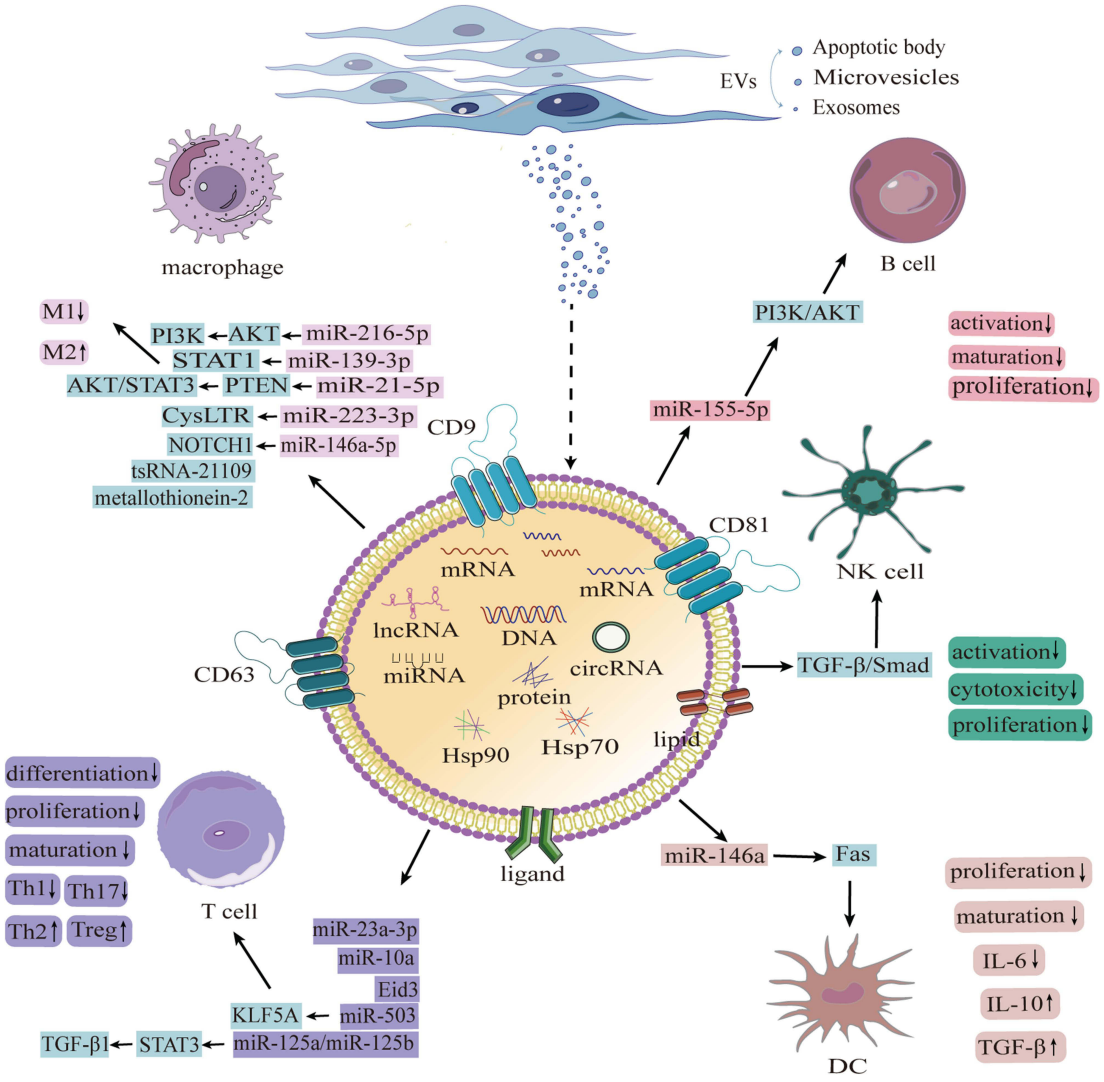

Figure 2 Role of MSC-derived EVs in regulating autoimmunity and inflammation. MSC-EVs suppress activation of B and NK cells, and reverse M1 phenotype into M2 phenotype. Further, MSC-EVs suppress DCs, leading to increased anti-inflammatory (TGF-β and IL-10) and decreased pro-inflammatory (IL-6) factors. MSC-EVs up-regulate Treg and Th2 but down-regulate Th1 and Th17 In addition to immunological cells, MSC-EV improves rheumatic disorders by acting on salivary gland cells, fibroblasts, and synovial cells and exerting anti-inflammatory effects.

cytokines, miRNAs, and peptides. MiR-216a-5p derived from hypoxia-preconditioned MSC-Exo has been found to repair spinal cord injury by regulating microglia M1/M2 polarization.[33] By preventing M1, MSC-EVs transfer of non-coding RNA tSNA-21109 has also been shown to dramatically reduce SLE.[34] Moreover, adipose tissue-derived MSC-EV (AD-MSC-EV) is demonstrated to improve healing, reduce matrix degradation, and switch synovial macrophages towards M2-type in knee OA via encapsulating microRNA.[35]

Table 1 Application of MSC-Derived Extracellular Vesicles in the Clinic

EV types	MSC source	Number of Patients	Biological Function	Disease	Reference
CF-CB-MS-EV	Human cord blood	Forty	Improve kidney function	Chronic kidney diseases	[26]
HaMSC-Exo	Human adipose	Seven	Lung lesions subsided significantly	COVID-19	[27]
BM-MSC- Exo	Human bone marrow	One	Symptoms such as diarrhea are relieved	Graft-versus-host disease	[28]
MSC-EV	Human placental	One	Reduces SSc	Systemic sclerosis	[29]

Table 2 Application of MSC-Derived EVs in Animal Research

EV Types	MSC Source	Animal Model	Encapsulated Active Substances	Biological Function	Regulatory Mechanism	Disease	Reference
MSC-Exo	Human bone marrow	Mice	Metallothionein-2	Reduces inflammation of the colon	Decreases IL-1β, IL-6 and TNF-α, increases CD206	Inflammatory bowel disease	[30]
HUC-MSC-Exo	Human umbilical cord	Mice	TRAF1	Improves steroid-resistant asthma	Regulates NF-κβ and PI3K/AKT signaling pathways	Steroid-resistant asthma	[31]
HUC-MSC-EV	Human umbilical cord	Mice	—	Treats chronic salpingitis	Promotes macrophage from M1 to M2, inhibits the TLR4 signaling pathway	Salpingitis	[32]
BMSC-Exo	Mouse bone marrow	Mice	miR-216a-5p	Repairs traumatic spinal cord injuries	Inhibits TLR4/NF-κβ and activates the PI3K/AKT signaling pathway	Traumatic spinal cord injury	[33]
HUC-MSC-sEV	Human umbilical cord	Rabbit	miR-100-5p	Reduces autoimmune dacryoadenitis	Promotes M2 polarization	Autoimmune dacryoadenitis	[36]
HUC-MSC-Exo	Human umbilical cord	Mice	—	Improves SLE	Promotes M2 macrophage and inhibits M1	SLE	[37]
HUC-MSC-sEV	Human umbilical cord	Rat	—	Improves OA	Suppresses M1 and increases M2	Osteoarthritis	[38]
MSC-EV	Rat bone marrow	Rat	miR-139-3p	Improves myocardial infarction	Inhibits the Stat1 pathway and encourages M2 polarization]	Myocardial infarction	[39]
MSC-Exo	Mouse bone marrow	Mice	—	Promotes renal self-recovery	Promotes the conversion of M1 to M2	Acute kidney injury	[40]
MSC-MV	Human umbilical cord	Rat	HGF	Reduces renal fibrosis	Promotes M2 macrophage polarization	Renal fibrosis	[41]
IPFP-MSC-Exo	Rat IPFP	Rat	—	Promotes anterior cruciate ligament reconstruction and intra-articular graft remodeling	Reduces M1 and promotes M2	Anterior cruciate ligament reconstruction	[42]
MSC-EV	Human Wharton's jelly	Mice	—	Improves acute lung injury	Promotes M2 polarization	Acute lung injury	[43]
P-EV	Mouse bone marrow	Mice	miR-21a-5p	Improves myocardial ischemia	Promotes M1 to M2 polarization	Myocardial ischemia-reperfusion	[44]
MSC-EV	Human pulp	Mice	—	Alleviates TNBS-induced colitis	Promotes M1/M2 infiltration	Crohn's Disease	[45]
MSC-EV	Human bone marrow	Rat	miR-15b, miR-19b, miR-22	Promotes bone regeneration	Down-regulates M1 and up-regulates M2	Rat calvaria defect	[46]
H@TI-EV	Human umbilical cord	Mice	—	Improves Type 1 Diabetes	Suppresses $CD4^+$ T cell, and induces the transition of macrophages from M1 to M2	Type 1 Diabetes	[47]
BMSC-Exo	Rat bone marrow	Rat	—	Promotes healing of diabetic wounds	Converts M1 to M2	Diabetes	[48]
BMSC-Exo	Human bone marrow	Rat	—	Promotes regeneration of blood vessels	Up-regulates PTEN, promotes M2, and inhibits M1	Diabetes	[49]
MSC-Exo	Mouse bone marrow	Mice	let-7a, miR-23a, miR-125b	Alleviates neurovascular dysfunction	Down-regulates TLR4/NF-κβ signaling pathway	Diabetic peripheral neuropathy	[50]
MSC-EV	Human bone marrow	Mice	miR-21-5p	Promotes cell proliferation	Reduces PTEN, activates Akt and STAT3, and facilitates M2	Non-Small-Cell Lung Carcinoma	[51]
MSC-EV	Human bone marrow	Mice	—	Improves neonatal brain damage	Down-regulates TNF-a and up-regulates the M2 marker]	Hypoxia-ischemia	[52]
BMSC-Exo	Male monkey bone marrow	Mice	—	Promotes myelin re-formation	Increases M2 and down-regulates TLR2/IRAK1/NF-κβ signaling pathway	Demyelinating diseases	[53]

(*Continued*)

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Table 2 (Continued).

EV Types	MSC Source	Animal Model	Encapsulated Active Substances	Biological Function	Regulatory Mechanism	Disease	Reference
HUC-MSC-sEV	Human umbilical cord	Rat	—	Reduces inflammation	Up-regulates IGFBP2/EGFR activates the EGFR/STAT3 pathway	Rat Spinal cord injury	[54]
MSC-Exo	Rat bone marrow	Rat	—	Improves acute brain injury	Reverses CysLT2R-ERK1/2-mediated microglial M1 polarization	Acute Brain Injury	[55]
BMSC-EV	Rat bone marrow	Rat	miR-223-3p	Reduces cerebral ischemia	Converts M1 to M2	Cerebral ischemia	[56]
ADMSC-EV	Mouse fat	Mice	—	Reduces spleen lymphocyte proliferation	Increases IL-10 and TGF-β, decreases IL-6	—	[57]
BMSC-MV	Mouse bone marrow	Mice	miR-146a	Improves survival of allografts	Promotes IL-12 expression and inhibits DC maturation	Allogeneic kidney graft	[58]
HUC-MSC-EV	Human umbilical cord	Mice	—	Improves dry eyes	Inhibits DCs and reduces Th17	Dry Eye Disease	[59]
MSC-EV	Human umbilical cord	Rat	—	Protects enal ischemia-reperfusion	Reduces TLR-2 and CX3CL1 expression	Renal ischemic reperfusion injury	[60]
HUC-MSC-sEV	Human umbilical cord	Sheep	—	Repair rotator cuff	Reduces T-cell proliferation	Rotator cuff	[61]
MSC-Exo	Human umbilical cord, mouse bone marrow	Mice	miR-223	Reduces aGVHD	Reduces donor T-cell migration	Acute Graft-versus-host disease	[62]
MSC-sEV	Mouse bone marrow	Mice	Eid3	Inhibits Th17 cells	Destroying the stability of RORγt	—	[63]
MSC-sEV	Human umbilical cord	Mice	—	Improves autoimmune uveitis	Inhibits Th1 and Th17	Autoimmune uveitis	[64]
HUC-MSC-sEV	Human umbilical cord	Rat	—	Improves the CIA	Inhibits T lymphocytes and increases Treg	Collagen-induced arthritis	[65]
MSC-Exo	Mouse fat	Mice	miR-21, miR-29	Improves acute colitis	Inducts Treg cells inhibit inflammatory cytokines, produces the anti-apoptotic effect	Inflammatory bowel disease	[66]
MSC-Exo	Human umbilical cord	Mice	—	Improves acute colitis	Increases TGF-β and IL-10, decreases IL-17 levels	Acute colitis	[67]
MSC-Exo	Mouse bone marrow	Mice	miR-125a, miR-125b	Alleviates colitis in mice	Reduces T cells on Stat3 and inhibits Th17	Colitis	[68]
MSC-Exo	Human umbilical cord	Mice	—	Improves multiple sclerosis	Increases Tregs and decreases Th1 and Th17	Multiple sclerosis	[69]
MSC-EV	Human umbilical cord	Mice	—	Alleviates experimental autoimmune encephalomyelitis	Induces Treg cells	Experimental autoimmune encephalomyelitis	[70]
SubQ-MSC-EV	Human subcutaneous fat	Mice	—	Inhibits T-cell proliferation	Reduces Th1/Th17 response	Crohn's disease	[71]
MSC-EV	Human bone marrow	Mice	miR-503	Destroys T cell proliferation and promotes glioma immune escape	Blocks KIF5A-dependent IL-7 signaling pathway	Glioma	[72]
MSC-EV	Human umbilical cord	Mice	—	Alleviates skin fibrosis in tumor-bearing cGVHD mice	Blocks Tfh and germinal center B cell action	Chronic graft-versus-host-disease	[73]
BMSC-Exo	Mouse bone marrow	Mice	miR-205-5p	Inhibits RA-FLS	Down-regulates MDM2 and Inhibits MAPK and NF-κβ	Rheumatoid arthritis	[74]

BMSC-EV	Human bone marrow	Rat	miR-34a	Improves RA	Inhibits cyclin II/ATM/ATR/p53 signaling pathway	Rheumatoid arthritis	[75]
MSC-Exo	Human bone marrow	Rat	circFBXW7	Inhibits RA-FLS inflammation	Inhibits miR-216a-3p and up-regulates HDAC4	Rheumatoid arthritis	[76–78]
BMSC-EV	Mouse bone marrow	Mice	miR-21	Inhibits mFLS	Inhibits TET1/KLF4 axis	Rheumatoid arthritis	[76–78]
MSC-Exo	Human bone marrow	Mice	miR-320a	Inhibits RA-FLS	Down-regulates CXCL9	Rheumatoid arthritis	[76–78]
HUC-MSC-Exo	Human umbilical cord blood	Rat	miR-451a	Targeting ATF2	Prevents FLS migration	Rheumatoid arthritis	[79]
GMSC-Exo	Human gingival fibroblasts	Mice	—	Inhibits joint deterioration	Inhibits synovial fibrosis	Rheumatoid arthritis	[80]
MSC-Exo	Mouse bone marrow	Mice	miR-150-5p	Improves RA	Inhibits MMP14 and VEGF	Rheumatoid arthritis	[81]
SMSC-Exo	Human synovial membrane	Mice	circEDIL3	Improves RA	Targeting miR-485-3p/PIAS3/STAT3 to regulate VEGF	Rheumatoid arthritis	[82]
SMSC- sEV	Synovial mesenchymal stem cells	Mice	miR-433-3p	Lessens arthritis	Increases VEGF expression	Rheumatoid arthritis	[83]
AMSC-EV	Mouse fat	Mice	IL-1ra	Improves RA	Inhibits IL-1 and TNFα	Rheumatoid arthritis	[84]
iMSC-Exo	Human iPSC	Mice	—	Improves RA	Reduces IL-17, IL-10, increases TGF-β1	Rheumatoid arthritis	[85]
ESC-MSC-sEV	Human Embryonic stem cell	Mice	—	Improves RA	Increases M2 and decreases IL-6	Rheumatoid arthritis	[86]
GMSC-Exo	Human gingival fibroblasts	Mice	—	Relieves RA, and reduces bone erosion	Inhibits IL-17RA-Act1-TRAF6-NF-κβ signaling pathway	Rheumatoid arthritis	[87]
ADMSC-Exo	Mouse fat	Mice	miR-146a, miR-155	Improves RA	Increases Treg cell	Rheumatoid arthritis	[88]
BMSC-Exo	Rat bone marrow	Rat	miR-223	Inhibits inflammatory factors	Down-regulates NLRP3	Rheumatoid arthritis	[89]
BMSC-EV	Human bone marrow	Mice	miR-378a-5p	Reduces inflammation	suppress the IRF1/STAT1 axis	Rheumatoid arthritis	[90]
BMSC-Exo	Mouse bone marrow	Mice	miR-16, miR-21	Relieves SLE progression	Targeting PDCD4 and PTEN	Systemic lupus erythematosus	[91]
HUC-MSC-Exo	Human umbilical cord	Mice	miR-146a-5p	Alleviates SLE-related DAH	Inhibits NOTCH1	Systemic lupus erythematosus	[92]
BMSC-EV	Mouse bone marrow	Mice	—	Reduces SLE	Inhibits T cell activation	Systemic lupus erythematosus	[93]
MSC-Exo	Mouse bone marrow	Mice	miR-196b-5p	Reduces SSc	Inhibits type I α2 collagen	Systemic sclerosis	[94]
BMSC-EV	Mouse bone marrow	Mice	miR-21a, miR-143, miR-27b, miR-29a, let-7	Reduces SSc	Reduces TGF-β1	Systemic sclerosis	[95]
HUC-MSC-Exo	Human umbilical cord	Mice	—	Reduces SSc	Down-regulates TGF-β/Smad signaling pathway	Systemic sclerosis	[96]
MSC-EV	Mouse bone marrow	Mice	miR-29a-3p	Improves skin fibrosis	Inhibits collagen type I and III levels	Systemic sclerosis	[97]
MSC-EV	Mouse bone marrow	Mice	—	Regulates anti-inflammatory and improves pulmonary fibrosis in mic	Up-regulates iNos, IL1ra, IL6 in ssEV, Up-regulates PGE2 protein in lsEV	Systemic sclerosis	[98]

(*Continued*)

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Table 2 (Continued).

EV Types	MSC Source	Animal Model	Encapsulated Active Substances	Biological Function	Regulatory Mechanism	Disease	Reference
HUC-MSC-Exo	Human umbilical cord	Mice	—	Relieves bleomycin-induced skin fibrosis	Balances M1/M2	Systemic sclerosis	[99]
BMSC-Exo	Human bone marrow	Mice	miR-214	Relieves bleomycin-induced skin fibrosis	Inhibits the IL-33/ST2 axis	Systemic sclerosis	[100]
MSC-EV	Human iPSC	Mice	miR-125b	Reduces salivary gland inflammation	Increases M2 and decreases Th17	Sjogren's syndrome	[101]
LG-MSC-Exo	Human labial gland	Mice	—	Reduces the inflammation of the exocrine gland	Inhibits Th17 cells, increases TGF-β, IL-10	Sjogren's syndrome	[102]
LG-MSC-Exo	Human labial gland	Mice	miR-125b	Restores the secretory function of the salivary gland	Targeting PRDM1 to inhibit plasma cells	Sjogren's syndrome	[103]
MSC-EV	Human iPSC	Mice	—	Reduces salivary gland inflammation	Reduces lymphocyte infiltration of B/ plasma cells	Sjogren's syndrome	[104]
OE-MSC-Exo	Mouse nasal cavity	Mice	—	Increases saliva flow rate	Secrets IL-6, promotes MDSC expansion and inhibits Th1/Th17	Sjogren's syndrome	[105]
OE-MSC-Exo	Mouse nasal cavity	Mice	—	Improves saliva flow rate	Inhibits the differentiation of Tfh cells, naive T cells, and plasma cells	Sjogren's syndrome	[106]
MSC-EV	Human iPSC	Mice	miR-21, miR-125b	Reduces salivary gland inflammation	Inhibits APC and T cell activation	Sjogren's syndrome	[107]
SHED-Exo	Human exfoliated deciduous teeth	Mice	—	Inhibits salivary gland cell apoptosis	Suppresses p-ERK1/2	Sjogren's syndrome	[108]
SHED-Exo	Human exfoliated deciduous teeth	Mice	—	Improves SS	Regulates the Akt/GSK-3β/Slug pathway	Sjogren's syndrome	[109]
DPSC-Exo	Human endodontic stem cell	Mice	—	Improves SS	Regulates the cAMP/PKA/CREB pathway	Sjogren's syndrome	[110]

Li's team discovers that subconjunctival injection of MSC-EV induces the transformation of macrophages into M2, which in turn alleviates autoimmune dacryoadenitis.[36] It is also very interesting to see how MSC-EVs control SLE macrophages, particularly in lupus nephritis. Our previous work has confirmed that hUC-MSC-Exo improved lupus nephritis by reshaping macrophage polarization to M2 in MRL/lpr mice.[37] Tang et al have reported that MSC-EV reduced the expression of CD14 and the pro-inflammatory cytokine IL-1, suppressed M1, and improved OA.[38] It is evident that MSC-EV inhibits the inflammatory response to illness.

According to more research, MSC-EV controls macrophages' capacity for repair in trauma-related illnesses. MSC-EVs carry miR-139-3p, which inhibits the Stat1 pathway and improves myocardial infarction by encouraging M2 macrophage.[39] Besides, BMSC-Exo-derived indoleamine 2,3-dioxygenase (IDO) participated in the tryptophan metabolism and promoted renal repair in acute renal injury by upregulating M2.[40] HUMSC-MVs improved renal fibrosis in ischemia partial nephrectomy rats by promoting M2 polarization via hepatocyte growth factor (HGF).[41] Additionally, MSC-Exos from the infrapatellar fat pad are demonstrated to promote tendon-bone repair by regulating M1/M2 polarization.[42] As a noninvasive strategy, inhalation of MSC-EVs has been documented to ameliorate acute lung injury by exerting anti-inflammatory and immunomodulatory effects.[43] The study by Li Qet al has implicated that platelet membrane-engineered EVs functioned to target immunomodulation of cardiac repair via delivering bioactive miRNAs into the cytoplasm and switching M1 polarization towards M2, suggesting the engineered EVs-based membrane fusion way to macrophages.[44]

Preconditioning MSCs with specific stimulation or gene editing technology may guide the future applications of MSC-EVs. Preconditioning MSCs with hypoxia and induction high expression of HIF-1α resulted in MSC-EVs with highly immunosuppressive and anti-inflammatory effects in experimental Crohn's disease.[45] Similarly, deferoxamine is documented to enhance the functions of MSC-EVs in effectively reprograming macrophage into M2 by activating the HIF-1α signaling pathway.[111] EVs from TNF-α-preconditioned MSCs can promote bone repair by decreasing M1 and boosting M2.[46] Engineered cytokine-primed MSC-EVs loaded hexyl 5-aminolevulinate hydrochloride (HAL) can regulate the PD-L1/PD-1 signaling pathway to suppress the activation of $CD4^+$T cells and induce the transition of macrophages from M1 to M2, thereby alleviating T1D.[47] Besides, the antibacterial and self-healing hydrogels loaded with BMSC-Exos are found to promote the healing of diabetic wounds by stimulating angiogenesis and transforming M2.[48] Moreover, melatonin-stimulated MSC-derived Exos enhance diabetic wound healing by inducing M2 polarization through the PTEN/AKT pathway.[49] Most interestingly, MSC-Exo is documented to improve peripheral neuropathy in a diabetic mice model by inducing M2 polarization, indicating that MSC-EVs also have significant advantages in regulating M1/M2 bias in treating diabetes-associated nerve injury.[50] However, MSC-EVs can accelerate tumor development by promoting M2 polarization in a hypoxic environment.[51] Accordingly, MSCs may be a double-edged sword. Taken together, MSC-EVs have significant impacts on regulating macrophage differentiation, polarization, activation, and functions in various inflammatory diseases.

In a brain injury mice model, MSC-EVs are documented to reduce the neuroinflammatory response, promote neural cell proliferation, and enhance oligodendrocyte maturation as well as the expressions of M2 markers of YM-1 and TGF-β.[52] Besides, MSC-Exos treatment is found to promote and inhibit neuroinflammation in the brain and spinal cord by inducing M2 polarization via the TLR2/IRAK1/NF-κβ signaling pathway.[53] Small EVs derived from four-dimensional-cultured MSCs (MSC-sEV) induce the transformation of M1 to M2 and inhibit inflammation in spinal cord injury rats by activating the IGFBP2/EGFR signal.[54] The cysteinyl leukotrienes (CysLTs) are a family of potent inflammatory mediators. MSC-Exos improve acute brain injury and inflammation by inhibiting the M1 polarization of the microglial cells via inactivating the CysLT2R-ERK1/2 signaling pathway.[55] MSC-Exos overexpressing microRNA-223-3p is reported to alleviate cerebral ischemia injury by inhibiting neuroinflammation and the M1 polarization of microglial cells.[56] As mentioned above, MSC-EVs exert significant effects on neuropathy, and spinal cord injury by regulating the M1/M2 balance of macrophage. Overall, by regulating macrophages, EVs, or exosomes from MSCs regulate inflammation, damage, and immunological disorders (Table 2 and Figure 2).

Regulation of Dendritic Cells (DCs) by MSC-EVs

DCs are also known as antigen-presenting cells.[112] DCs in many illnesses are regulated by MSC-EVs (Table 2 and Figure 2). TGF-β and IL-6 are critical in inflammatory and immune diseases.[113,114] According to a study by Shahir, M.'s

group, AD-MSC-Exo promotes the generation of tolerogenic DC, IL-10, and TGF-β generation but reduces IL-6 in mice.[57] Another study has also documented that mature DC treated with MSC-EV resulted in a large rise in TGF-β and a decrease in IL-6, which suggests that MSC-EV is critical in limiting DC maturation.[115] Furthermore, MSC-EVs are demonstrated to alleviate allergic rhinitis by enhancing the generation of IL-10 and Treg cell but reducing Th2 response.[116] In addition, BMSC-derived microvesicles (BMSC-MVs) can enhance the longevity of transplanted kidneys by increasing the expression of micro-146a in DCs.[58] As is well known, the complexity of the dendritic structure of DCs reflects their maturation ability. It has been implicated that the administration of MSC-EV led to significantly decreased intricacy of DC dendrites in mice corneas, slower DC maturation, and reduced dry eye symptoms in mice.[59] Consequently, MSCs and MSC-EVs have great potential for modulating DC maturation and DC-mediated immunological effects.

Regulation of Natural Killer (NK) Cells by MSC-EVs

Bone marrow lymphocytes give rise to natural killer (NK) cells, which are engaged in immunological and inflammatory responses.[117] MSC-EVs-derived miRNA-155 and miRNA-146 have been shown to primarily block the G0 and G1 phases of the NK cell cycle.[118] Besides, MSCs-Exos derived from the fetal liver have been well documented to prevent NK cell proliferation through the TGF-β/Smad signaling pathway.[119] There was an increase in NK cells in the wounded kidneys and splenic organs following renal ischemia-reperfusion, according to another study.[60] However, reduced severity of renal ischemia-reperfusion injury was found due to a significantly decreased proportion of NK cells and reduced expressions of TLR-2 and CX3CL1 in kidneys after the intravenous infusion of MSC-EV.[60] It has been found that the biological effects of bone marrow-derived MSCs (BMSC) were superior to adipose-derived MSCs (ADMSC) in rat kidney transplantation.[120] However, the study has reported no improvement in renal function from the EVs of either source, whereas the ADMSC-EV promoted T cells and NK cells infiltration into the kidneys, accelerating the progression of end-stage renal disease.[120] Hence, MSC-EVs may control the biological activity of NK cells, thereby compromising their immunomodulatory role. Nonetheless, the source of MSC-EVs should be seriously considered before application. Table 2 and Figure 2 illustrate how MSC-EV controls NK cells.

Modulation of Adaptive Immune Cells by MSC-EVs

Regulation of T Cells by MSC-EVs

T cells are involved in adaptive immunity.[121] According to many studies, MSC-EV can regulate T cells. MSC-EVs are reported to inhibit $CD4^+$T cell expansion and Th1 response.[122] There are also studies that show MSC-EVs dramatically lower T cell activation and improve Treg cell activity.[123] In several disorders, MSC-EV can regulate T-cells. For example, F. Jenner et al found that Small extracellular vesicles (sEVs) derived from hUC-MSC markedly reduced T-cell proliferation in the context of rotator cuff repair.[61] MSC-Exo-delivering miR-223 could hinder donor T cell migration in mice of aGVH.[62] Regulatory cells (Tregs) are necessary to keep the peripheral immunological environment steady. Foxp3 is a widely recognized transcription factor responsible for Treg differentiation. Yeganeh, A. and his team have revealed that MSC-EVs increased $CD4^+CD25^+FOXP3^+$ T cells.[124] Pro-inflammatory cell subpopulation Th17 causes harm to tissues. RORγt is a pivotal transcription factor for pro-inflammatory Th17 cells. MSC-EVs can inhibit Th17 cells by destabilizing RORγt.[63] As a result, MSC-EVs are essential for controlling T cell differentiation, proliferation, and function.

Multiple research results have revealed that MSC-EVs can be used to treat other autoimmune diseases. Small EVs from MSCs are found to alleviate autoimmune uveitis by suppressing Th1 and Th17 cells but promoting Treg activation.[64] HUC-MSC-EV can reduce T-lymphocytes, while decreasing Th17 cells and increasing Treg cells, thereby ameliorating collagen-induced arthritis (CIA).[65] Several studies have also shown that MSC-Exo regulated the Th17/Tregs balance and alleviated colitis.[66–68] sEVs from programmed death receptor (PD-L1)-modified MSCs are demonstrated to foster Tregs differentiation and extend allograft survival.[125] MSC-Exo has also been shown to decrease Th1- and Th17-associated cytokines while enhancing Tregs in multiple sclerosis.[69] Additionally, MSC-EVs attenuate experimental autoimmune encephalomyelitis by stimulating Treg cells.[70] As previously mentioned, our research team has determined that MSC-Exo improved SLE via Treg augmentation.[37] Other studies have shown that MSC-EVs suppress the Th17 cell response to modify SLE.[126] Accordingly, MSC-EVs may improve the condition by balancing Th17/Treg and Th1/Th2 in autoimmune diseases.

MSC-EVs maintain immune tolerance and immune microenvironment homeostasis by regulating T-cell bioactivity. However, not all tissue-derived MSCs and their EVs inherently possess robust anti-inflammatory properties. MSC-EVs extracted from the mesenteric tissue of Crohn's disease patients had diminished capacity to inhibit T cells, unlike MSCs and their EVs sourced from subcutaneous adipose tissue (SubQ), which effectively suppressed T-cell, IFN-γ, and IL-17a.[71] Moreover, miR-503 loaded by MSC-EV is found to facilitate glioma immune escape.[72] Therefore, the varying disease conditions, diverse tissue sources, and other factors may influence or reshape the action of MSC-EVs. In summary, MSC-EVs can control T cell activation, proliferation, and polarization (Table 2 and Figure 2).

Regulation of B Cells by MSC-EVs

B cells develop into a vast quantity of plasma cells, which subsequently generate autoantibodies.[127] MSC-EVs have a regulatory effect on B cells (Table 2 and Figure 2). There is evidence that MSC-EVs inhibit Tfh's interaction with reproductive center B cells in vivo.[73] Additionally, BMSC-derived Exos can inhibit B cells by regulating the expression of mRNA genes related to B cell maturation and differentiation.[128] MSC-EVs exert immunosuppressive effects by suppressing B cell.[118] Recent research has revealed that MSC-EV inhibited B cells by regulating the PI3K-AKT signaling pathway.[129] In addition, BMSC-EV can prevent B cells apoptosis in chronic lymphocytic leukemia.[130] However, the study by Carreras-Planella, Let al has discovered that MSCs could confer an immunomodulatory effect on B cells independent of MSC-EV.[131] Future research is required to figure out the precise functions and mechanisms of the various MSC-EV subtypes in controlling B cells.

Regulatory Role and Mechanism of MSC-EVs in Rheumatic Diseases

MSC-EVs and RA

The main feature of RA is the presence of multiple joints.[132] UC-MSCs have shown good efficacy and tolerance in patients with RA.[133] When RA patients received intravenous UC-MSC injections, their symptoms and other indications improved, according to a domestic clinical trial.[133] Liming Wang et al conducted a three-year prospective phase I/II study using UC-MSC cells in combination with DMARDs, and most patients showed significant improvement in joint symptoms with fewer side effects. Two of these patients, including one elderly male and young female, recovered from joint deformities after 3 years of UC-MSC use, suggesting that UC-MSC cells combined with DMARDs may be a safe and effective long-term treatment for RA patients.[134] Several studies have pointed to the involvement of MSC-EV in RA (Table 2 and Figure 3). Fibroblast-like synovial cells (FLSs) are involved in joint lesions. MSC-EVs influence RA by interacting with FLSs and promoting joint repair by delivering bioactive molecules to the damaged joints. For instance, in a CIA mouse model, miR-205-5p delivered by BMSC-Exos dramatically reduced arthritis by regulating double minute 2 (MDM2) in FLSs.[74] According to Su. et al, lncRNA HAND2-AS1 loaded via MSC-Exos inhibited RA-FLS.[135] Besides, miR-34a delivered by BM-MSC-EVs could inhibit RA-FLS and enhance inflammation by targeting cyclin I through the ATM/ATR/p53 signaling pathway.[75] Meng, H. Y. et al found that miRNA-124a-overexpressed MSC-derived EVs prevented RA-FLS by affecting the cell cycle G0/G1 conversion.[136] Other bioactive molecules such as circFBXW7, microRNA-21, and microRNA-320a loaded by MSC-Exo were also demonstrated to inhibit FLS, suggesting critical roles of non-coding RNAs delivered by MSC-Exo in RA.[76–78] High levels of AFT2 expression encouraged RA-FLS invasion.[137] Exosomes loaded with miR-451a that are generated from hUC-MSC bind to ATF2 to prevent FLS.[79] Joints can be destroyed by activated synovial fibroblasts. Activation of synovial fibrogenesis and other joint deterioration are inhibited by gingival mesenchymal stem cells (GMSC) and their exosomes have been demonstrated by the development of a hybrid human/mouse model of synovitis.[80] Taken together, MSC-EVs significantly affect the development and progression of arthritis and joint damage in RA by delivering bioactive mediators involved in RA-FLS proliferation, cell cycle regulation, and inflammation.

Matrix metalloproteinases (MMPs) are crucial enzymes involved in RA that promote synovium invasion and cartilage damage by degrading the extracellular matrix. MSC-Exos-miR-150-5p alleviated RA by reducing the expression of targeted genes of MMP14 and VEGF.[81] Interleukin-27 (IL-27) is overexpressed in RA. According to L. Ma et al, MSC-derived exosomes induced by IL-27 exacerbate RA mainly via upregulating MMP3 expression through the miR-206/L3MBTL4

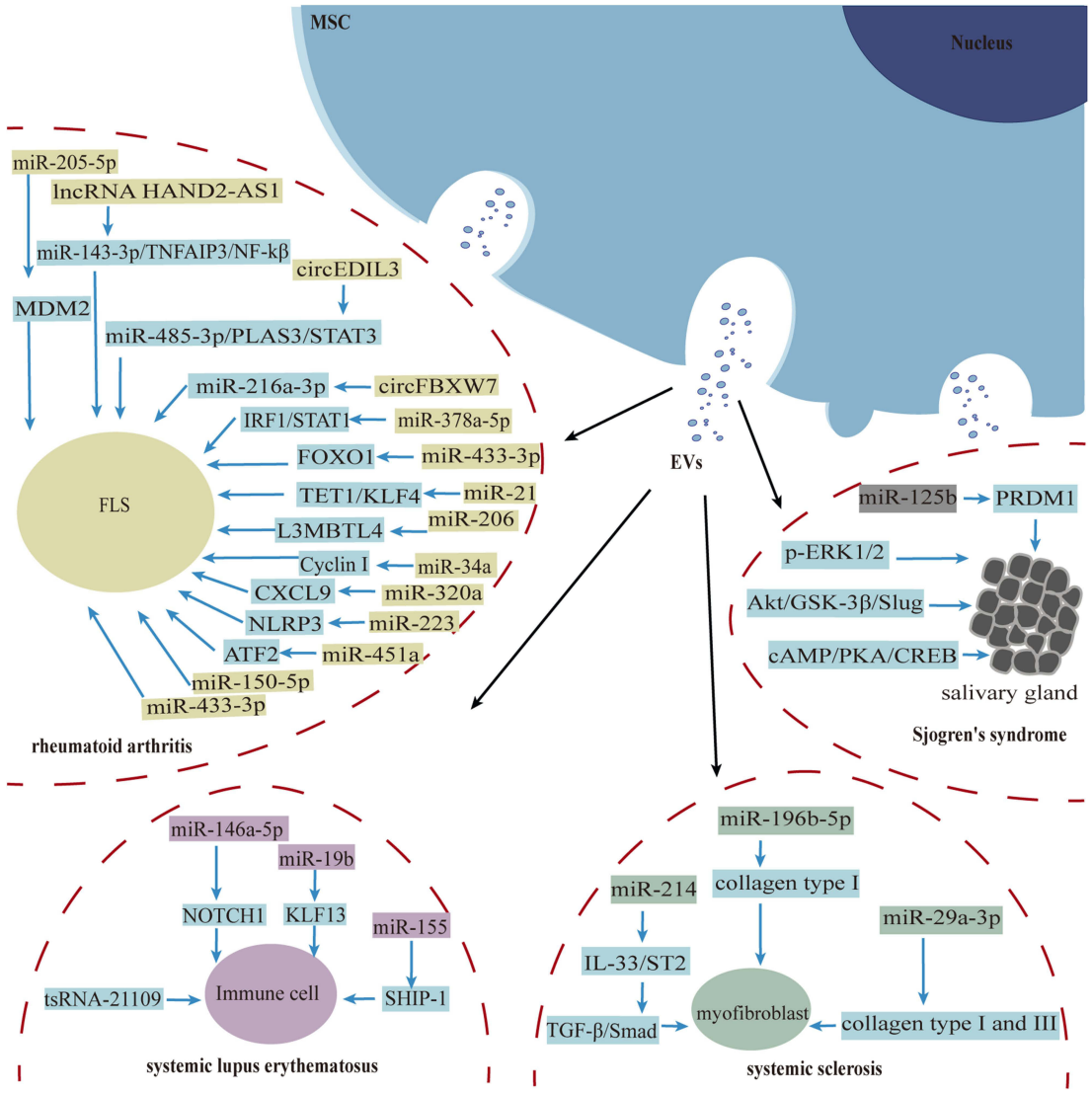

Figure 3 Regulatory effects and mechanisms of MSC-EVs in common rheumatic diseases. MSC-EV improves RA by inhibiting inflammation in FLS through some miRNAs. In addition to miRNA delivery, MSC-EV also acts on salivary gland bodies through several pathways to improve dry mouth, dry throat, or other symptoms in SS mice models. In addition, MSC-EV improves skin sclerosis in SSc or alleviate pulmonary fibrosis by delivering miRNAs. Similarly, in SLE, MSC-EV exerts immunomodulatory and anti-inflammatory effects by interacting with immune cells through complicated mechanisms.

axis.[138] This provides us with a new target for the treatment of R, which can be performed by inhibiting IL-27. It has been well documented that inflammation promotes angiogenesis, which thus aggravates RA. Zhang et al revealed that circEDIL3 delivered by MSC-Exos from human synovium alleviates RA by inhibiting VEGF production via the miR-485-3p/PIAS3/STAT3 signaling pathway.[82] Many investigations conducted in the last few years have discovered that iron death inducers can exacerbate synovial angiogenesis and cause RA-FLS, while SMSCs-sEV that overexpresses MiR-433-3p increases VEGF expression and lessens the severity of arthritis.[83] AMSC-derived EV suppressed inflammation by delivering IL-1ra and inhibiting IL-1 and TNF-α secretions in an RA mouse model.[84] Exosomes from iMSCs reduce IL-17, IL-10, and IL-1β while increasing TGF-β1, polarizing Th2 and M2, and improving RA.[85] Small extracellular vesicles derived from MSCs decreased inflammatory cytokine IL-6 and increased M2, which reduced joint inflammation in CIA mice. However, the researchers did not find any statistically significant differences in the therapeutic effects of MSC-sEVs at low and high dosages.[86] It is evident that managing inflammation is essential to managing RA.

In RA, MSC-EVs can regulate immune disorders. Gingival MSC-derived exosome (GMSC-Exo) regulated the Th17/Treg balance to alleviate RA.[87] Additionally, mouse adipose MSC-Exo-derived miR-146a/miR-155 up-regulated Treg

cells and relieved joint inflammation.[88] According to Huang et al, miR-223 encapsulated in MSC-Exos could alleviate arthritis by suppressing macrophage-induced inflammation via targeting NLRP3.[89] T cells are a major factor in RA pathogenesis. MSC-EV has shown a more potent inhibitory effect on RA pathogenesis as compared to MSC. This was attributed to the MSCs' IFN-β-induced suppression of CD4 T cells.[139] To suppress the IRF1/STAT1 axis and reduce inflammation in RA animals, BMSC-EV distributes miR-378a-5p.[90] Accordingly, MSC-EVs and the encapsulated bioactive molecules can control RA (Table 2 and Figure 3).

MSC-EVs and SLE

Chronic inflammation, autoimmune diseases, and numerous organ damage are the final results of SLE, an autoimmune illness marked by excessive immune cell proliferation, activation, and abundance of autoantibodies.[140] According to recent clinical research, UC-MSCs are safe and effective for lupus patients via significantly increasing GARP-TGFβ complexes and reducing CD27IgD double-negative B cells.[141] We should continue to monitor the impact of MSC-secreted vesicles on the therapy of early SLE as, as per F. Guo et al, hUC-MSC transplantation reduces B-cell proliferation in the early peripheral blood of SLE mice, which is useful for the treatment of early SLE.[142] Umbilical cord blood MSCs (UC-BSC)-derived exosomes exerted immunomodulatory and anti-inflammatory effects in SLE by regulating Th17/Treg balance through the miR-19b/KLF13 axis.[143] According to our earlier research, hUC-MSC-Exos can reduce SLE by modifying M2 polarization and increasing Treg cells.[37] Another work has also reported that MSC-Exos-derived miR-16 and miR-21 alleviated SLE by regulating macrophage polarization.[91] Dou et al have demonstrated that tsRNA-21109 encapsulated by MSC-Exo alleviated SLE by inhibiting M1 macrophage polarization.[34] Chen et al have also pointed out that microRNA-146a-5p delivered by hUC-MSC-EVs significantly improved SLE-related diffuse alveolar hemorrhage by promoting anti-inflammatory M2 polarization via targeting the NOTCH1 signal.[92] Similarly, hUC-MSCs and hUC-MSC-EVs could exert immunoregulatory effects by upregulating Th17 and increasing TGF-β1 in SLE.[126] UCMSC-Exos can suppress miR-155 in B cells and raise SHIP-1 levels, which encourages B cell death and reduces SLE.[144] Apoptotic vesicles formed from MSCs, such as EVs, block TCR signaling to prevent T cell activation and IL-2 release. Additionally, apoVs have been shown to not harm mice's organs, which helps to alleviate SLE.[93] Accordingly, MSC-EVs work similarly to MSCs and provide SLE patients with a different kind of biological therapy (Table 2 and Figure 3).

MSC-EVs and SSc

SSc manifests as vascular lesions and fibrosis of the skin or organs.[145] MSC-EVs can serve as miRNA carriers and exert immunomodulatory in SSc (Table 2 and Figure 3), such as MSC-EVs-derived miRNA clusters, miR-196b-5p, and miR-29a-3p.[94–97] BMSC-EVs-delivering miRNA clusters are documented to suppress SSc by regulating the WNT signal and TGF-β signal.[95] TGF-β1 is part of the process of tissue fibrosis. MSC-Exo has been demonstrated to improve SSc by downregulating the TGF-β/Smad signaling pathway.[96] Remarkably, EVs produced from AD-MSC outperformed parental cells in terms of enhancing myofibroblasts.[146] Additionally, IFNγ-primed MSCs-EVs confer immunoregulatory function and improve lung fibrosis by upregulating iNOS, IL1ra, IL6, and PGE2.[98] Regulation of M1/M2 macrophage balance is another effect of MSC-Exos in treating SSc.[99] Interstitial lung disease (ILD) is a manifestation of severe lung involvement by SSc. Patients with SSc were found to benefit from placental MSC-EV, according to a recent clinical case report. After undergoing traditional medical treatment, the patient still needed oxygen therapy; however, after utilizing MSC-EV, the patient's symptoms, including dyspnea, dramatically improved, necessitating no longer oxygen therapy. Additionally, a lung CT scan revealed a considerable reduction in fibrosis (Table 1).[29] In systemic sclerosis (SSc), interleukin (IL)-33 functions as a pro-inflammatory cytokine and stimulates fibrosis. By delivering miR-214 and inhibiting the IL-33/ST2 axis, BMSC-Exos reduce cutaneous fibrosis.[100] Altogether, MSC-EVs as a whole exhibit a therapeutic impact on SSc.

MSC-EVs and SS

SS is characteristic of loss of exocrine glands structure and function, which results in symptoms such as dry mouth, dry eyes, and swallowing difficulty.[147] The progression of SS is associated with Th17/Treg.[148] In pSS, UCMSC-Exos primarily inhibit CD4 T cell growth by blocking the G0/G1 phase and limiting the cells' ability to enter the S phase, which in turn balances

Th17/Treg.[149] Salivary gland inflammation was successfully reduced by EV derived from early passaged iMSCs, which also reduced Th17 and boosted M2.[101] MSC and MSC-Exos derived from the labial gland (LG) can ameliorate murine SS by suppressing Th17 but up-regulating Treg.[102] Moreover, it has also been found that LG-MSC-Exos-derived miR-125b could alleviate SS by inhibiting plasma cell and targeting PRDM1.[103] According to reports, EV isolated from human induced pluripotent stem cells (IPSCs) can activate APC, suppress Tfh and Th17 cells, and relieve SS.[104] Under pathological microenvironment, IL-6 is essential for enhancing the suppressive ability of myeloid-derived suppressor cells (MDSC). Olfactory MSC-derived exosomes (OE-MSC-Exo) are demonstrated to increase MDSC proliferation and attenuate SS via activating the IL-6/Jak2/Stat3 pathway.[105] OE-MSC-Exo-derived PD-L1 is documented to alleviate SS by inhibiting Tfh response.[106] Additionally, the contents of MSC-EVs may vary according to the parent MSCs. In an SS mouse model, Lee et al have found that iPSC-MSC-EVs at an earlier stage exhibited higher immunomodulatory potencies than iPSC-MSC-EVs at a later stage.[107] Salivary secretion was stimulated by exosecreted by human exfoliated deciduous teeth (SHEDs), which suppressed p-ERK1/2 activation and glandular cell death.[108] According to another study, ZO-1 expression regulated by the Akt/GSK-3β/Slug pathway is the primary mechanism by which Exo generated from human deciduous teeth can enhance SS and increase paracellular permeability of glandular epithelial cells.[109] A transmembrane estrogen receptor is called GPER. Exosomes produced from endodontic stem cells (DPSCs) stimulate the cAMP/PKA/CREB pathway via GPER to enhance salivary gland epithelial cell activity.[110] The regulatory mechanisms of MSC-EVs in SS are summarized in Table 2 and Figure 3, which lays a theoretical foundation of MSC-EVs for future clinical applications in SS.

Conclusions

The impacts of MSC-EVs with various origins on controlling both innate and adaptive immune responses are methodically covered in this review. In particular, we summarize the underlying mechanisms of MSC-EVs in rheumatic diseases, primarily including RA, SLE, and SS. MSC-EVs have exhibited great potentials in inhibiting inflammation and excessive immune responses, thereby defending against organ and tissue damage. Compared to MSCs, MSC-derived EVs are less immunogenic, safe, and simple to utilize and store. Nevertheless, we need to focus on some issues including quality standards of MSC-EVs, intra-batch and inter-batch repeatability, and characterization and standards of MSC-EVs for a clinical-grade reagent. Besides, further research on the pharmacokinetics, long-term safety, targeted homing mechanism, and active and nonactive components of MSC-EVs needs further exploration.

Data Sharing Statement

The data supporting this review are from previously reported studies and datasets, which have been cited. The processed data are available from Donghua Xu upon request.

Author Contributions

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

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Disclosure

All authors declare no conflicts of interest.

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