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Application of extracellular vesicles derived from mesenchymal stem cells as potential therapeutic tools in autoimmune and rheumatic diseases

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ABSTRACT

Mesenchymal stem cells (MSCs) have been proven to have superior potential to be used as therapeutic candidates in various disorders. Nevertheless, the clinical application of these cells have been restricted because of their tumorigenic properties. Increasing evidence has established that the valuable impacts of MSCs are mainly attributable to the paracrine factors including extracellular vesicles (EVs). EVs are nanosized double-layer phospholipid membrane vesicles contain various proteins, lipids and miRNAs which mediate cell-to-cell communications. Due to their inferior immunogenicity and tumorigenicity, as well as easier management, EVs have drawn attention as potential cell-free replacement therapy to MSCs. For that reason, herein, we reviewed the recent findings of researches on different MSC-EVs and their effectiveness in the treatment of several autoimmune and rheumatic diseases including multiple sclerosis, inflammatory bowel disease, rheumatoid arthritis, osteoarthritis, osteoporosis, and systemic lupus erythematosus as well as Sjogren's syndrome, systemic sclerosis and other autoimmune diseases.

Abbreviations: MSCs, Mesenchymal stem cells; EVs, Extracellular vesicles; BM, Bone marrow; Exos, exosomes; MVs, microvesicles; ILVs, Intraluminal vesicles; MVBs, Multivesicular bodies; HSP, Heat-shock protein; MS, Multiple sclerosis; CNS, Central nervous system; ADMSC, Adipose tissue-derived MSC; TMEV, Theiler's murine encephalomyelitis virus; Huc, Human umbilical cord; PBMCs, Peripheral mononuclear blood cells; RRMS, Relapsing-remitting MS; EAE, Encephalomyelitis; IBD, Inflammatory bowel disease; UC, Ulcerative colitis; CD, Crohn's disease; DSS, Dextran sulfate sodium; TNBS, 2,4,6-trinitrobenzenesulfonic acid; TRAF6, TNF receptor-associated factor 6; IRAK1, IL-1 receptor-associated kinase 1; OE, Olfactory ecto; RA, Rheumatoid arthritis; RA-FLS, RA fibroblast-like synoviocytes; CXCL9, CXC chemokine ligand 9; CIA, Collagen-induced arthritis; MMP14, Matrix metalloproteinase 14; VEGF, Vascular endothelial growth factor; OA, Osteoarthritis; CIOA, Collagenase-induced OA; SMSC, Synovial membrane-derived MSC; DMM, Destabilization of medial meniscus; TMJ, Temporomandibular joint; GelMA, Gelatin methacrylate; ECM, Extracellular matrix; ESC, Embryonic stem cell; IPFP, Infrapatellar fat pad; OP, Osteoporosis; HLU, Hind limb unloading; GPNMB, Glycoprotein nonmelanoma clone B; CMS, Cyclic mechanical stretch; SLE, Systemic lupus erythematosus; DAH, Diffuse alveolar hemorrhage; SS, Sjögren's syndrome; NOD, Non-obese diabetic; LGMSCs, Labial gland-derived MSCs; cGVHD, Chronic graft-versus-host disease.

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1. Introduction

Autoimmune diseases are multiple chronic conditions in which immunologic self-tolerance is lost and contribute to destruction of own body's tissue by mistake [1]. Rheumatic disorders are also a collection of autoimmune diseases characterized by the inflammation and damage of joints, muscles, bones, and internal organs [2]. These conditions are a main cause of severe disability, organ failure and mortality, forcing high medical costs [3]. However, the management of these patients remains an important challenge. Hence, early treatment is key to limit damage that is extremely essential.

Mesenchymal stem cells (MSCs) have recently gained significant attention of researchers as promising approaches to treat various human diseases via their differentiation and self-renewal capacity, paracrine effects and immunomodulatory properties [4,5]. MSCs are originated from various sources including bone marrow (BM), peripheral blood, adipose tissue and umbilical cord as well as dental pulp, endometrial polyps, placenta and Wharton's jelly [4,6,7]. MSCs isolated from adult human tissues, such as BM, have been the most commonly used sources for treatment of different diseases. Nonetheless, therapeutic application of these cells has been restricted due to their tumorigenic features, low proliferative capacity and cell contents. Besides, highly invasive and painful procedures for obtaining MSCs from these sources are related to major morbidity and risk of infection [8–10]. Furthermore, proliferation and differentiation ability of MSCs are associated with the availability, condition, age, health, and genetic of the donor tissue [11,12]. Therefore, clinicians require novel approaches to use the beneficial capability of the MSCs in treatment of diseases while removing cell transplantation obstacles.

According to the current knowledge, therapeutic efficacy of MSCs are largely mediated by paracrine factors including proteins, lipids, miRNAs and mRNAs released by extracellular vesicles (EVs) [13]. EVs are lipid membrane delimited particles recognized as important mediators of intercellular communication. There exist three main types of EVs, comprising exosomes (Exos), microvesicles (MVs), and apoptotic bodies [14,15]. EVs display a great safety profile and can be stored without losing function in comparison with their parental MSCs [16]. As a result, these EVs are of great importance as potential cell-free-based therapeutic candidates in treatment of different human disorders.

Considering these advantages, we attempted to provide a summary of several recent preclinical and clinical studies which investigated the efficiency of EVs in autoimmune and rheumatic diseases including multiple sclerosis, inflammatory bowel disease, rheumatoid arthritis, osteoarthritis, osteoporosis, systemic lupus erythematosus and Sjogren's syndrome as well as systemic sclerosis and other autoimmune disorders.

2. Extracellular vesicles

EVs (Fig. 1) are nanosized spherical lipid membranous particles enclosing proteins, nucleic acids, lipids and metabolites which have complex functions in cell-to-cell communication [6,17]. EVs can be isolated from almost all cell types and found in body fluids such as blood, urine, saliva, amniotic fluid and semen as well as cerebrospinal fluid and breast milk. These particles are also detectable in tissues and cell culture supernatants [18,19]. EVs play important roles in various biological processes including stem cell differentiation, regulation of immune system, angiogenesis, tissue regeneration and blood coagulation as well as autophagy and reproductive system biology [6,20].

Exo is the most popular subtype of EVs which arise from early endosomes [21,22]. The early endosome goes through a maturation process to become a circular late endosome and results in the formation of cargo-containing intraluminal vesicles (ILVs) within the endosome lumen which are also called multivesicular bodies (MVBs) [23,24]. The MVBs can fuse with the plasma membrane to release their contents into extracellular environment as well as undergo lysosomal transition for degradation of their contents in the form of Exos [25,26]. Exos, with a size ranging from 50 nm to 100 nm, can be obtained with an ultracentrifugation above 100,000*g* and −80 °C is the optimal temperature for their storage that maintains their functions [27]. They were shown to carry cell-specific cargos including DNAs, RNAs, lipids, and proteins such as tubulin, actin, and actin-binding proteins, annexins and Rab, as well as heat-shock protein 70 (HSP70) and HSP90 that control different aspect of trafficking, docking, and fusion with the plasma membrane [6,28]. Tetraspanins including CD9, CD63, CD81, or CD82 have a broad distribution in membrane of Exos and have been widely used as exosomal markers [29].

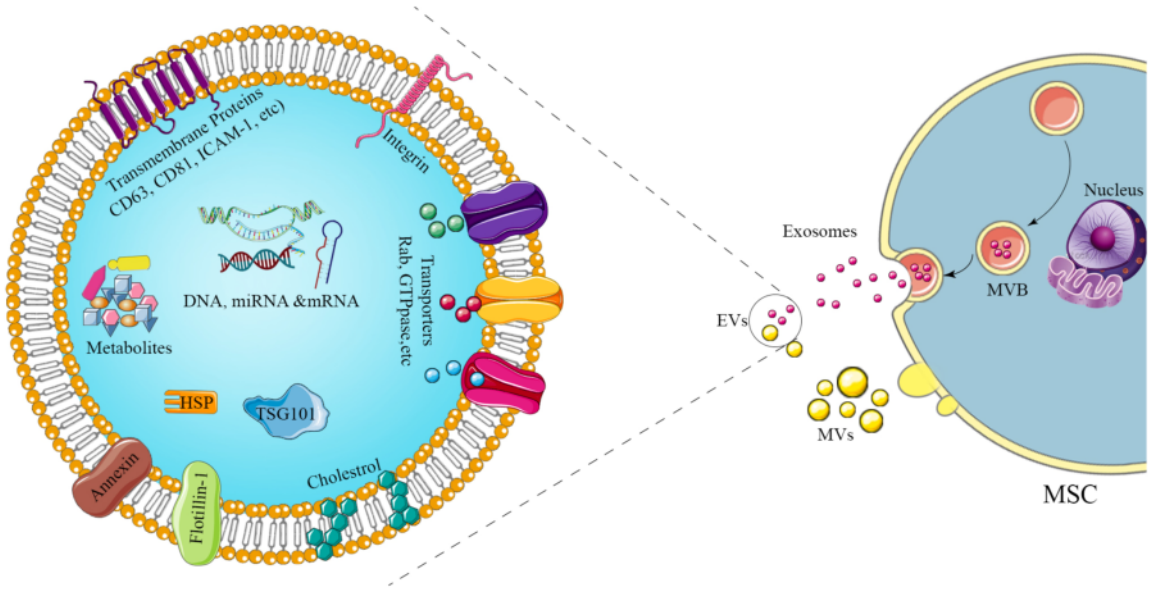

Fig. 1. Biogenesis and structure of extracellular vesicles (exosomes an microvesicles). MSC, mesenchymal stem cell; MVB, multivesicular bodies; MVs, microvesicles; EVs, extracellular vesicles.

3. Therapeutic potential of MSC-EVs in autoimmune and rheumatic diseases

Increasing researches have recently evaluated the efficiency of MSC-EVs in various autoimmune and rheumatic disorders therapy, which are discussed in the following parts (Table 1). Furthermore, Fig. 2 demonstrates several mechanisms by which MSC-EVs involve in treatment of these diseases.

3.1. MSC-EVs and multiple sclerosis

Multiple sclerosis (MS) is a complex and potentially disabling autoimmune disorder of the central nervous system (CNS) with neurodegenerative properties that causes a great economic and societal burden [30,31]. Accumulating data have recently shown the beneficial effects of MSC-EVs in MS therapy. Laso-García and coworkers (2018) have recently investigated the impact of intravenous injection of MSC-EVs derived from adipose tissue (AD) in murine model of progressive MS infected with Theiler's murine encephalomyelitis virus (TMEV) [32]. They reported that AD-MSC-EVs could improve motor deficits via immunoregulatory properties, reducing brain atrophy and enhancing remyelination. Baharlooi et al. (2020), indicated that human umbilical cord (huc)-MSC-Exos could more effectively suppress proliferation of peripheral mononuclear blood cells (PBMCs) in relapsing-remitting MS (RRMS) patients than their parental MSCs [33]. In another study, MSC-Exos was covalently conjugated with a high affinity aptamer (LJM-3064) toward myelin and administrated into autoimmune encephalomyelitis (EAE) mice model of MS [34]. According to the results, the severity of the disorder was effectively diminished by suppressing inflammatory responses (decreasing Th1 population and elevating Treg cells) and demyelination lesion region in CNS. Besides, a recent research has showed that BM-MSC-Exo therapy has important role in enhancing remyelination and modulating neuroinflammation through modulating microglia from M1 to M2 in CNS in two EAE and cuprizone murine models of MS [35]. Similarly, BM-MSC-Exos have been proven to have the capacity in attenuating neuroinflammation and CNS demyelination in rats with EAE by modulating the polarization of microglia from M1 to M2 phenotype [36]. It has also been found that placental MSC-EVs promoted motor function and myelin regeneration in EAE- affected MS murine models in comparison with untreated control group [37]. Furthermore, Giunti et al (2021) have recently evaluated the role of nine miRNAs shuttled by IFN-γ-primed MSC-EVs in modulating neuroinfammation in EAE- induced mice model. The findings of this study revealed that miR-467f and miR-466q could reduce the inflammatory phenotype of microglia via regulating p38 MAPK signaling and preventing the expression Map3k8 and Mk2 genes [38].

3.2. MSC-EVs and inflammatory bowel disease

Inflammatory bowel disease (IBD) is an intractable autoimmune disease includes ulcerative colitis (UC) and Crohn's disease (CD) that significantly affect quality of life in these patients [39,40]. Recently, the therapeutic effects of MSC-EVs have been studied in IBD models. For example, Heidari et al. (2021), evaluated the potential of AD-MSC-Exo therapy in mice model of acute form of dextran sulfate sodium (DSS)-induced colitis [41]. These researchers showed a downregulation in inflammatory cytokines and upregulation in Treg population which led to alleviation of colitis in the animal model. Furthermore, intravenous administration of AD-MSC-Exos in DSS-induced IBD mouse model could promote functional recovery, reduce inflammation and improve epithelial regeneration as well as maintain intestinal barrier integrity [42]. A recent research conducted by Li et al. (2020) also revealed that both AD-MSCs and AD-MSC-EVs have similar immunosuppressive and anti-inflammatory impacts in murine model of DSS-induced colitis [43]. It has also been revealed that intravenous transplantation of huc-MSC-Exo-derived miR-378a-5p could repair colitis and alleviate IBD in murine model of DSS-induced colitis by regulating macrophage pyroptosis via inhibiting the activation of NLRP3 inflammasomes [44]. Additionally, the therapeutic effects of exosomal miR-326 released from huc-MSCs were proved using the DSS-induced IBD mice model, in which treatment led to relieved colitis via inhibiting neddylation [45]. Intraperitoneal transplantation of huc-MSC-Exos-secreted TSG-6 also enhanced IBD symptoms in murine models by repairing the mucosal barrier, suppressing pro-inflammatory cytokines and maintaining balance between Th2 and Th17 cells [46]. Huc-MSC-Exos also could exert immunosuppressive function *in vitro* and in mice with DSS-induced colitis by regulating inflammation mechanism [47]. These Exos have also alleviated DSS-induced IBD in mice through ubiquitination [48] and modulation of IL-7 expression in macrophages [49]. Tolomeo and coworkers (2021) carried out a comparative study between MSCs and MSC-EVs, with and without priming with pro-inflammatory cytokines, to treat IBD in mice model of DSS-induced colitis [50]. Their findings showed that cytokine-primed MSC-EVs could markedly decrease intestinal fibrosis and angiogenesis and improve intestinal epithelial function by regulating the polarization of macrophages from M1 to M2 phenotype and elevating Treg population as compared with parental MSCs. Likewise, BM-MSC-EVs attenuated DSS-induced UC by elevating M2 macrophages [51,52]. It has also been elucidated that BM-MSC-EVs containing miR-146a could play a protective role in rats with 2,4,6-trinitrobenzenesulfonic acid (TNBS)-induced colitis by inhibiting TNF receptor-associated factor 6 (TRAF6) and IL-1 receptor-associated kinase 1 (IRAK1) [53]. In another study conducted by Tian et al. (2020), olfactory ecto (OE)-MSC-Exos significantly relieved the severity of disorder by downregulating Th1 and Th17 populations and upregulating Tregs in murine model of DSS-induced colitis [54]. Besides, it was examined by Duan et al. (2020) that EVs from human placental MSCs could relieve TNBS-induced colitis in mice by suppressing inflammation and oxidative stress [55]. It has also been proposed that EVs released from MSCs primed with pro-inflammatory stimuli and overexpress hypoxia-inducible factor 1-alpha and telomerase, have better therapeutic effects in mice with TNBS-induced colitis. Their findings showed that the EVs could decrease fibrosis and inflammation by increasing the level of M2 macrophages [56].

3.3. MSC-EVs and type-1 diabetes mellitus

Type 1 diabetes mellitus (T1DM) is a complex autoimmune disorder that occurs as a result of pancreatic beta-cells destruction by T cells [57]. T1DM is affected by genetic, immune system and environmental factors [58,59]. In a report by Nakano et al. (2016), the effectiveness of intravenous injection of rat BM-MSC-Exos was evaluated in streptozotocin (STZ)-diabetic mice [60]. According to this study, BM-MSC-Exos had similar functions to those BM-MSs and could enhance the cognitive impairments in the mice model through regeneration of impaired neurons and astrocytes. In another study, STZ-diabetic mouse models were divided into two groups; a group received intraperitoneal administration of AD-MSC-Exos and a non-treated control group [61]. The treated group ameliorated of autoimmune reactions by significant elevation of Tregs, IL-4, IL-10, TGF-β and reduction of IL-17 and IFN-γ. Additionally, Shigemoto-kuroda et al. have found in their study [62] that MSC-EVs could prevent islet inflammation by suppressing Th1 and Th17, considerably up-regulating the plasma insulin concentrations, and efficiently postponing the manifestation of T1DM in murine models.

3.4. MSC-EVs and rheumatoid arthritis

Rheumatoid arthritis (RA) is one of the most common chronic autoimmune disorders characterized by synovial inflammation, leading to progressive joint damage, disability and shortened quality of life in these patients [63,64]. The favorable therapeutic impacts of MSC-EVs have been demonstrated in RA therapy via their anti-fibrotic, anti-apoptotic, anti-inflammatory and pro-regenerative effects [65].

Table 1
Therapeutic potential of mesenchymal stem cell-derived extracellular vesicles (MSC-EVs) in autoimmune and rheumatic diseases.

Injury	Animal model	Infusion method	Origin of EVs	Dose of injection	Outcome	Reference
Inflammatory bowel disease (IBD)	Rat	Intravenous injection	BM-MSC-EV-derivedmiR-146a	100 μg	Attenuate experimental colitis by targeting TRAF6 and IRAK1	[53]
IBD	Mice	Intraperitoneal injection	BM-MSC-EVs	50 μL	Attenuate dextran sodium sulfate-induced ulcerative colitis by promoting M2 macrophage polarization	[51]
IBD	Mice	Intraperitoneal injection	AD-MSC-EVs	–	Have immunosuppressive and anti-inflammatory functions	[43]
IBD	Mice	Intravenous injection	Huc-MSC-Exo-derived miR-378a-5p	1 mg	Attenuate colitis by regulating macrophage pyroptosis via the NLRP3 pathway	[44]
IBD	Mice	Intravenous injection	AD-MSC-Exos	300 μg	Protect mice from DSS-Induced IBD by promoting intestinal-stem-cell and epithelial regeneration	[42]
IBD	Mice	Intraperitoneal injection	AD-MSC-Exos	100 μg	Alleviate acute colitis by Treg cell induction and inflammatory cytokine reduction	[41]
IBD	Mice	Intravenous injection	Huc-MSC-Exo-derived miR-326	1 mg	Inhibit neddylation to relieve IBD	[45]
IBD	Mice	Intraperitoneal injection	Huc-MSC-Exo-derived TSG-6	200 μg	Protect against IBD through restoring mucosal barrier repair and intestinal immune homeostasis	[46]
IBD	Mice	Intravenous injection	MSC-Exos	–	Reduce murine colonic inflammation via a macrophage-dependent mechanism	[52]
IBD	Mice	Intravenous injection	Olfactory ecto-MSC-Exos	60 μg	Ameliorate colitis via modulating Th1/Th17 and Treg cells	[54]
IBD	Mice	Intravenous injection	Huc-MSC-Exos	400 μg	alleviate IBD through the modulation of IL-7 expression in macrophages	[49]
IBD	Mice	–	MSC-EVs	–	Resulted in polarization of intestinal macrophages towards and anti-inflammatory phenotype	[50]
IBD	Mice	–	Huc-MSC-Exos	200 μg	Possess immunosuppressive effect *in vitro* and exhibit a therapeutic capability in vivo through suppressing inflammation mechanism	[47]
IBD	Mice	–	Placental MSC-EVs	200 μg	Alleviate experimental colitis in mice by inhibiting inflammation and oxidative stress	[55]
IBD	Mice	Intraperitoneal injection	Human dental pulp-MSC-EVs	50 μg	Decrease fibrosis and inflammation by increasing the level of M2 macrophages	[56]
Type 1 diabetes mellitus (T1DM)	Mice	Intravenous injection	BM-MSC-Exos	0.5 μg	Improve the cognitive impairments of by repairing damaged neurons and astrocytes	[60]
T1DM	Mice	Intraperitoneal injection	AD-MSC-Exos	50 μg	Exert ameliorative effects through increasing Tregs, IL-4, IL-10, TGF-β and reduction of IL-17 and IFN-γ.	[61]
T1DM	Mice	Intravenous injection	MSC-Exos	30 μg	Attenuate immune responses	[62]
Osteoarthritis (OA)	Mice	Articular injection	Synovial MSC-Exo-derived miR-155-5p	30 μL	Prevent OA via enhancing proliferation and migration, attenuating apoptosis, and modulating extracellular matrix secretion in chondrocyte	[79]
OA	Mice	Articular injection	BM-MSC-Exos	250 ng	Protect cartilage and bone from degradation in osteoarthritis	[73]
OA	Rat	Articular injection	BM-MSC-Exos	10^{10} /ml	Prevent OA by regulating synovial macrophage polarization	[74]
OA	Mice	Articular injection	iMSC-Exos and SMMSC-Exos	10^{10} /ml	iMSC-Exos exerted a stronger stimulatory effect on chondrocyte migration and proliferation than did SMMSC-Exos	[76]
OA	Rat	Articular injection	SMSC-Exo-derived miR-140-5p	100 μg	Enhance cartilage tissue regeneration and prevent OA of the knee	[77]
OA	Mice	Articular injection	Polydactyly BM-MSC-Exos	–	Alleviate OA by promoting chondrocyte proliferation	[84]
OA	Mice	Articular injection	LPS-primed SMSC-ECVs	10^{11} /ml	Inhibit ECM degradation and prevent OA	[78]
OA	Mice	Articular injection	Embryonic-MSC-Exos	10^{6} /ml	Alleviate OA through balancing synthesis and degradation of cartilage extracellular matrix	[80]
OA	Rat	Joint cavity injection	BM-MSC-Exos	40 μg	Promote cartilage repair and extracellular matrix synthesis, as well as alleviate knee pain	[81]
OA	Rat	Joint injection	Huc-MSC-Exo-derived miR-26a-5p	250 ng	Alleviate OA via down-regulation of PTGS2	[82]
OA	Mice	–	MSC-Exo-derived KLF3-AS1	–	Elevate chondrocyte proliferation and inhibit apoptosis through miR-206/GIT1 axis	[85]
OA	Rat	Articular injection	Embryonic stem cell-derived MSC-Exos	100 μg	Reduce pain and repair osteoarthritic TMJs by attenuating inflammation and restoring matrix homeostasis	[86]
OA	Mice	–	BM-MSC-Exo-derived miR-92a-3p	500 μg	Enhance chondrogenesis and suppress cartilage degradation via targeting WNT5A	[87]
OA	Rabbit	Subcutaneous injection	ECM/GelMA/ BM-MSC-Exos	–	Restored chondrocyte mitochondrial dysfunction, enhanced chondrocyte migration, and polarized the synovial macrophage response toward M2	[88]
OA	Mice	Articular injection	IPFP-MSCs-Exo-derived miR-100-5p	10^{10} /ml	Protect articular cartilage and ameliorate gait abnormalities via inhibition of mTOR	[89]
OA	Rat	Articular injection	AD-MSC-Exos	100 μg	Facilitate cartilage injury repair and alleviate OA	[90]
Osteoporosis (OP)	Rat	–	BM-MSC-Exo-derived miR-150-3p	–	Promote osteoblast proliferation and differentiation in osteoporosis	[93]
OP	Rat	Intravenous injection	GPNMB-modified BM-MSC-EVs	100 μg	Attenuate bone loss in an ovariectomized rat model of OP	[97]

(*continued on next page*)

Table 1 (*continued*)

Injury	Animal model	Infusion method	Origin of EVs	Dose of injection	Outcome	Reference
OP	Mice	Intraperitoneal injection	Huc-MSC-Exos	–	Induce osteogenesis and prevent OP	[95]
OP	Mice	Intravenous injection	BM-MSC-Exos	0.1 mL	Inhibit RANKL-induced osteoclastogenesis through the NF-κB signaling pathway	[99]
OP	Rat	Intravenous injection	Epimedium-Preconditioned BM-MSC-EVs derived miR-27a-5p	100 ng	Stimulate osteogenesis by targeting Atg4B-mediated autophagy	[100]
OP	Rat	Intravenous injection	BM-MSC-Exos derived miR-186	10^{13} /ml	Promote osteogenesis through hippo signaling pathway in OP	[102]
OP	Rat	–	BM-MSC-EVs derived miR-20a	–	Promote the osteointegration of porous titanium alloy by enhancing osteogenesis via targeting BAMBI	[103]
OP	Rat	–	Huc-MSC-Exos derived miR-1263	–	Prevent apoptosis in disuse osteoporosis	[94]
Multiple sclerosis (MS)	Mice	Intravenous injection	AD-MSC-EVs	25 μg	Attenuate motor deficits through immunomodulatory actions, diminishing brain atrophy and promoting remyelination	[32]
MS	–	–	Huc-MSC-Exos	–	Suppress proliferation of activated PBMCs	[33]
MS	Mice	Intravenous injection	MSC-Exos armed with high affinity aptamer	200 μg	Produced synergistic immunomodulatory properties and remyelination effect	[34]
MS	Rat	Intravenous injection	BM-MSC-EVs	100 and 400 μg	Attenuate inflammation and demyelination of the central nervous system in EAE rats by regulating the polarization of microglia	[36]
MS	Mice	Intravenous injection	Placental MSC-EVs	10^{7} or 10^{10} /ml	Promote myelin regeneration	[37]
amyotrophic lateral sclerosis (ALS)	Mice	intravenous or intraperitoneal injection	IFNγ-primed MSC-EVs	–	Affect neuroinfammation possibly through specific immunomodulatory miRNAs acting on microglia	[38]
Rheumatoid arthritis (RA)	Mice	Intraperitoneal injection	BM-MSC-Exo-derived miRNA-150-5p	50 μg	Decrease migration and invasion and inhibiting angiogenesis *in vitro* and alleviating the symptoms of RA by the Modulation of MMP14 and VEGF	[71]
RA	Rat	–	BM-MSC-Exo-derived miR-192-5p	50 mg	Delays inflammatory response	[67]
RA	–	–	BM-MSC-Exo-derived miR-320a	–	Regulate RA-FLSs activation by suppressing CXCL9	[68]
RA	Rat	Intravenous injection	BM-MSC-EV-derived miR-34a	75 μg	Reduce RA inflammation via the cyclin I/ATM/ATR/p53 axis	[66]
RA	Mice	Intravenous injection	BM-MSC-EVs	–	Exert an anti-inflammatory role on T and B lymphocytes independently of MSCs priming	[69]
Sjögren's syndrome (SS)	Mice	–	Labial gland- MSC-Exos	50 μg	Ameliorate SS by modulating the balance of Treg and Th17 cells	[112]
SS	Mice	Intravenous injection	Olfactory ecto- MSC-Exos	100 μg	Ameliorate SS by modulating the function of myeloid-derived suppressor cells	[113]
Systemic lupus erythematosus (SLE)	Mice	Intravenous injection	Huc-MSC-Exos	100 μg	Regulate macrophage polarization to attenuate SLE-associated diffuse alveolar hemorrhage	[108]
SLE	–	–	MSC-Exo-derived tsRNA-21109	–	Alleviate SLE by inhibiting macrophage M1 polarization	[109]
Systemic Sclerosis (SSc)	Mice	Intravenous injection	IFNγ-Primed-MSC-EVs	250 ng	Improved lung fibrosis by modulating anti-inflammatory and anti-fibrotic markers	[117]
SSc	Mice	Intravenous injection	MSC-EV-derived miR-29a-3p	100 μg	Downregulate the expression of several pro-fibrotic, remodeling and anti-apoptotic factors as well as methylases	[116]
SSc	Mice	Subcutaneous injection	MSC-Exo-derived miR-196b-5p	20 μg	Suppress skin fibrosis	[115]
SSc	Mice	–	BM-MSC-EVs	15 μg	Alleviate SSc pathogenic changes by regulating the WNT and TGFβ signaling pathways	[118]
SSc	Mice	–	MSC-Exos	–	Ameliorate dermal fibrosis in bleomycin-induced scleroderma	[119]
Chronic graft-versus-host-disease (cGVHD)	Mice	Intraperitoneal injection	Huc-MSC-EVs	100 μg	Prevent skin fibrosis by suppressing the activation of macrophages and B cells immune response	[122]

Recently, Wu et al. (2020), have reported that miR-34a derived from BM-MSC-EVs, suppressed inflammation of RA via inhibiting the cyclin I/ATM/ATR/p53 signaling in rat model [66]. They also indicated that miR-34a could inhibit proliferation and upregulate apoptosis in RA fibroblast-like synoviocytes (RA-FLS) *in vitro*. In addition, a study provided evidence that transplantation of miR-192-5p derived from BM-MSC-Exos could alleviate joint destruction and inflammatory responses in rat model of RA and also inhibited inflammation *in vitro* [67]. Meng and Qiu reported that exosomal miR-320a secreted from BM-MSCs could inhibit the activation, migration, and invasion of RA-FLSs *in vitro* through suppressing CXC chemokine ligand 9 (CXCL9) [68]. The results of this study also revealed that the miR-320a alleviate arthritis and bone damage in collagen-induced arthritis (CIA) mouse models. In another study conducted by Cosenza et al. (2018), the immunomodulatory effects of BM-MSC-EVs, including Exos and microparticles (MPs), were compared in CIA mouse model [69]. According to the results, Exos had more anti-inflammatory effects on T and B lymphocytes as compared with MPs. These Exos were also shown to diminish the level of $CD4^{+}$ and $CD8^{+}$ T cell populations and increase Treg cells independently of MSCs primed by IFN-γ. It has also been established that miR-146a/miR-155

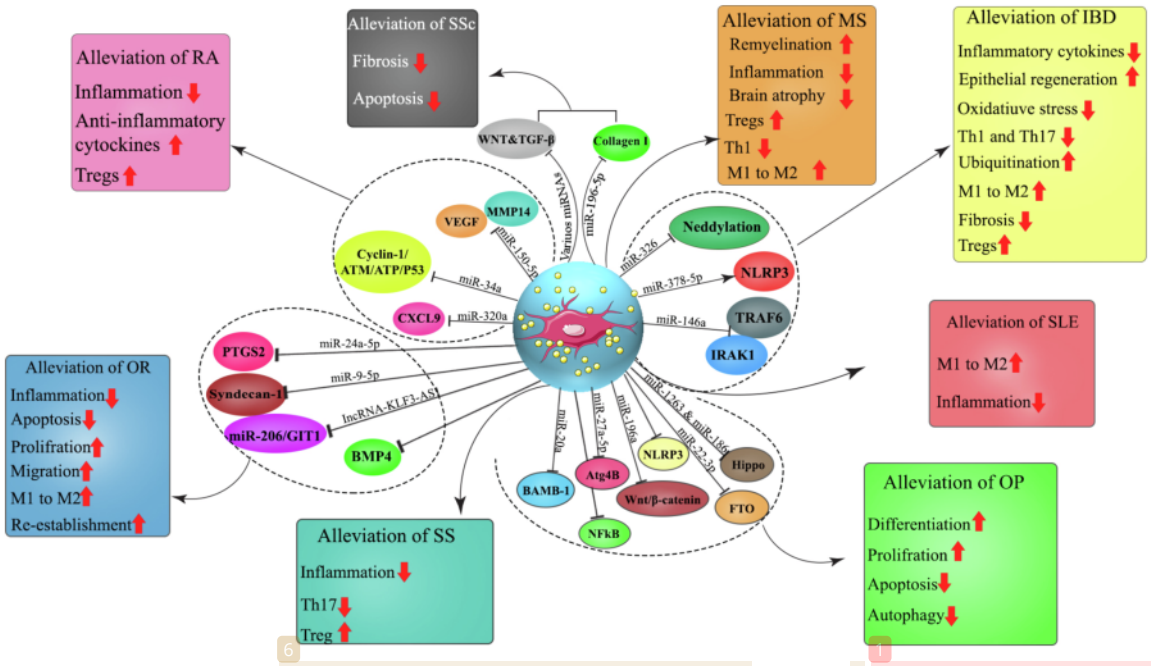

Fig. 2. The mechanisms through which mesenchymal stem cell-derived extracellular vesicles (MSC-EVs) participate in treatment of autoimmune and rheumatic diseases. MS, multiple sclerosis; IBD, inflammatory bowel disease; RA, rheumatoid arthritis; OA, osteoarthritis; OP, osteoporosis; SLE, systemic lupus erythematosus; SS, Sjogren's syndrome; SSc, systemic sclerosis.

derived from BM-MSC-Exos improved the immunomodulatory effects in CIA mouse model through elevation of Tregs and anti-inflammatory cytokines [70]. Moreover, the great efficacy of exosomal miR-150-5p derived from BM-MSCs were shown in treatment of RA through decreasing migration and invasion of RA-FLSs and downregulating angiogenesis by targeting matrix metalloproteinase 14 (MMP14) and vascular endothelial growth factor (VEGF) *in vitro* [71]. These Exos were also decreased joint destruction and alleviate symptoms in CIA mouse model.

3.5. MSC-EVs and osteoarthritis

Osteoarthritis (OA) is the most common rheumatic disorder worldwide, characterized by progressive cartilage degradation, synovial inflammation, and sub-chondral bone thickening [72]. Increasing number of researches have examined the therapeutic properties of MSC-EVs in OA. For instance, the similar chondroprotective and anti-inflammatory impacts of murine BM-MSC-derived MPs and Exos have shown in treatment of collagenase-induced OA (CIOA) mouse model via re-establishing chondrocyte homeostatic state, preventing chondrocytes from apoptosis and modulating macrophages towards anti-inflammatory phenotype [73]. Additionally, a recent research elucidated that intra-articular injection of BM-MSC-Exos could alleviate OA damage in rat model by regulating synovial macrophage from M1 to M2, reducing inflammatory cytokines and damage of articular cartilage [74]. It has also been proposed that BM-MSC-EVs improve cartilage regeneration and have anti-inflammatory effects in TNF-alpha-stimulated OA *in vitro* [75]. Zhu et al. (2017) also indicated that transplantation of induced pluripotent stem cell-derived MSC-Exos had great therapeutic impact in CIOA mouse model in comparison with synovial membrane-derived MSC (SMSC)-Exos by stimulating chondrocyte migration and proliferation [76]. Besides, it has been revealed that miR-140-5p-overexpressing SMSC-Exos enhance cartilage tissue regeneration and inhibit knee joint damage in OA rat models [77]. In a recent report, LPS-primed SMSC-EVs were shown to facilitate knee cartilage repair in OA mouse model by increasing the proliferation and migration of chondrocytes and suppressing the apoptosis of these cells [78]. Wang et al. (2020) demonstrated that SMSC-Exo-miR-155-5p could improve the chondrocyte proliferation and migration, reduce apoptosis, modulating cartilage extracellular matrix (ECM) secretion, and promote cartilage repair in mouse model of OA [79]. In another study conducted by Wang and coworkers (2017), intra-articular administration of embryonic stem cell (ESC)-MSC-Exos relieved cartilage damage and reduced matrix degradation in the destabilization of the medial meniscus (DMM) mouse model through balancing the synthesis and degradation of ECM [80]. Furthermore, BM-MSC-Exos were shown to have regenerative effects in cartilage injury, ECM synthesis, and could relieve knee pain in rats with OA [81]. Recently, Jin et al. (2020) found that BM-MSC-Exo-derived miR-26a-5p could alleviate OA damage in vivo by downregulation of PTGS2 [82]. These authors also proposed in another animal study that exosomal miR-9-5p released from BM-MSCs have chondroprotective potential and could alleviate OA and decrease inflammation via targeting syndecan-1 in rat model of OA [83]. Polydactyly BM-MSC-Exos have also demonstrated superior ability in enhancing chondrocyte formation and attenuating OA in murine model via BMP4 signaling pathway [84]. In another animal investigation by Yubao Liu et al. (2018), MSC-Exo-derived lncRNA KLF3-AS1 was injected into CIOA mice. Results indicated elevation in chondrocyte proliferation and inhibition of apoptosis through miR-206/GIT1 axis [85]. One other group found that MSC-Exos suppress pain and enhance temporomandibular joint (TMJ) regeneration in OA rat model via reducing inflammation, restoring matrix homeostasis, improving proliferation and matrix synthesis, while decreasing apoptosis [86]. The results from a study by Mao et al (2018) who administrated BM-MSC-Exo-derived miR-92a-3p into CIOA-induced mice model indicated that these vesicles inhibited cartilage degradation and regulated homeostasis by targeting WNT5A [87]. Chen and coworkers (2019) loaded BM-MSC-Exos into three dimensional printed ECM/ gelatin methacrylate (GelMA) scaffolds and

implanted the scaffolds subcutaneously into rabbit model of osteochondral defect. Results suggested that these scaffolds have beneficial roles in early treatment of OA by restoring cartilage mitochondrial dysfunction, improving chondrocyte migration, and modulating the synovial macrophage polarization towards M2 [88]. Additionally, intra-articular injection of miR-100-5p from infrapatellar fat pad (IPFP) MSC-Exos could alleviate cartilage injury in mice with OA through reducing chondrocyte apoptosis, regulating cartilage homeostasis and preventing mTOR-autophagy pathway [89]. Intra-articular transplantation of AD-MSC-EVs bind to chitosan oligosaccharides have also shown to have great impacts on cartilage regeneration in rats with OA by ameliorating the migration of chondrocytes and downregulating apoptosis [90]. Furthermore, an *in vitro* study discovered that Exos and MVs from AD-MSCs reduce inflammation and oxidative stress in OA osteoblasts [91].

3.6. MSC-EVs and osteoporosis

Osteoporosis (OP) is a common complication in rheumatic diseases characterized by imbalance between bone resorption and formation, contribute to deterioration of bone tissue and elevated risk of fracture [92]. Qiu et al. (2021) evaluated the contribution of miR-150-3p from BM-MSC-Exos to attenuate OP in rats [93]. These researchers exhibited that there was a noticeable promotion in osteoblast proliferation and differentiation and suppression in apoptosis. In 2020, Yang et al. demonstrated that huc-MSC-Exo-derived miR-1263 exerted anti-apoptotic effects in hind limb unloading (HLU)-induced OP by Mob1/Hippo axis [94]. Huc-MSC-Exos have also shown to have role in osteogenic induction and OP inhibition in mice model [95]. Moreover, AD-MSC-Exos were identified to relieve diabetic OP by downregulating NLRP3 inflammasome in osteoclasts in rats [96]. Glycoprotein non-melanoma clone B (GPNMB)-modified BM-MSC-EVs were also effective to reduce the ovariectomized-induced bone loss in a rat model of OP through regulating Wnt/β-catenin signaling pathway [97]. In 2020, a study provided evidence that administration of BM-MSC-EV-derived miR-22-3p is an effective approach to improve the osteogenic differentiation in ovariectomized-induced OP in mice by preventing FTO [98]. Cyclic mechanical stretch (CMS)-modified BM-MSC-Exos are also associated with the inhibition of OP in mouse models via reducing the activation of NF-κB signaling pathway [99]. In another study conducted by Li and coworkers (2021), miR-27a-5p released from epimedium-preconditioned BM-MSC-EVs were successfully induced osteogenic differentiation and led to alleviation of ovariectomized-induced OP in rats through targeting Atg4B autophagy [100]. In addition, miR-196a derived from BM-MSC-Exos contributed to enhancement of osteoblastic differentiation by targeting Dkk1 to activate Wnt/β-catenin signaling [101]. As described by Li et al (2021) in their article, miR-186 delivered by BM-MSC-Exos could also improve osteogenesis by hippo signaling pathway in rats with ovariectomized-induced OP [102]. BM-MSC-EVs overexpressing miR-20a also exerted a great effect on osteoporotic bone defects through targeting BAMBI in rats with OP [103]. Moreover, it has recently been proposed that circRNAs from BM-MSC-Exos could affect the improvement of OP in these patients [104]. It has also been proposed that BM-MSC-Exos enhanced the osteoblast proliferation by MAPK signaling pathway *in vitro* [105].

3.7. MSC-EVs and systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is a chronic autoimmune disorder characterized by the immune cell hyper-activity and accumulated autoantibodies which lead to multiple organ injury [106,107]. A number of evidences have established that MSC-EV transplantation is beneficial strategy for treatment of SLE. In a recent study, Chen et al. (2021) have established that huc-MSC-Exos altered macrophage response from M1 to M2 that diminished SLE-related diffuse alveolar hemorrhage (DAH) and inflammatory responses in mice [108]. Similarly, tsRNA-21109 derived from MSC-Exos have revealed to have potential role in alleviating SLE by inhibiting macrophage M1 polarization and reducing inflammatory cytokines *in vitro* [109].

3.8. MSC-EVs and Sjogren's syndrome

Sjogren's syndrome (SS) is a chronic systemic autoimmune disorder characterized by inflammation and functional impairment in the salivary and lacrimal glands [110,111]. With a murine model of non-obese diabetic (NOD), intravenous administration of Labial gland-derived MSCs (LGMSCs) and LGMSCs-Exos exerted beneficial effects in treatment of SS via reducing inflammatory infiltration in the salivary glands and restoring salivary gland secretory function as well as inhibiting the differentiation of Th17 cells, and inducing of Treg cells [112]. Likewise, another animal study demonstrated that OE-MSC-Exos significantly reduced disease severity in murine SS by enhancing the suppressive function of myeloid-derived suppressor cells [113].

3.9. MSC-EVs and systemic sclerosis

Systemic sclerosis (scleroderma) is an unusual autoimmune rheumatic condition defined by diffuse fibrosis and vasculopathy in the skin, joints, and internal organs such as pulmonary, heart, kidneys, and etc [114]. Baral et al. (2021) have revealed that administration of MSC-Exos overexpressing miR-196b-5p could markedly prevent bleomycin-induced dermal fibrosis in a SSc mouse model through suppressing type I collagen expression in fibroblast [115]. The beneficial effects of MSC-EVs have also investigated in murine model of HOCl-induced SSc [116]. These EVs alleviated the clinical symptoms by regulating skin and lung fibrosis, remodeling and anti-apoptotic factors via releasing miR-29a-3p. Besides, a recent finding has indicated the enhanced therapeutic effect of IFN-γ-primed MSC-EVs in murine SSc model through regulating anti-inflammatory and anti-fibrotic markers [117]. Jin et al. (2021) have also recently reported that miRNAs from BM-MSC-EVs relieved SSc in mice by modulating the WNT and TGF-β signaling [118]. Exos from MSCs can also be involved in attenuating dermal fibrosis in mice with bleomycin-induced SSc via decreasing the TGF-β/Smad signaling [119].

3.10. MSC-EVs and other autoimmune diseases

It has been reported that MSC-Exos could reduce psoriasis-associated inflammation in a imiquimod-induced mouse model of psoriasis through inhibition of complement activation in the stratum corneum and decrease in IL-17 [120]. Another study suggested that MSC-Exos could increase the survival and alleviate the damage of chronic graft-versus-host disease (cGVHD) via downregulating Th17 cell population and upregulating Tregs [121]. Furthermore, MSC-EVs inhibit skin fibrosis in murine cGVHD through regulating the macrophage activation and reducing B cells immune reactions [122].

4. Conclusion and future perspective

In recent decades, MSC-EVs have shown prominent implications in treatment of various diseases due to their several features such as regenerative capacity, reducing inflammation and immunomodulatory functions. As compared with their parental cells, EVs could offer a safer and promising therapeutic candidate in diseases therapy because of their beneficial properties including lower tumorigenicity, immunogenicity, and easier management. However, the safety and efficiency of these EVs have to go through appropriate clinical studies before being marketed to patients. Several clinical trials involving EVs have been registered on https://www.clinicaltrials.gov. Moreover, the underlying mechanism in EVs biogenesis, pharmacokinetics and biodistribution needs more extensive researches before this approache can be applied to clinical therapy. Accumulating data have also demonstrated that modified or engineered EVs may be valuable therapeutic options for decreasing

unwanted adverse events in the future clinical use of MSC-EVs. Consequently, there is no doubt that EVs hold excessive potential in addressing cell biology problems, and moreover, it is vital to improve new prospects for their clinical application as therapeutic and diagnostic tools.

Authors' contributions

HH and SAJ performed and wrote the manuscript; DOB, WKA and MNS collected the references, designed the table and figures; LT and RM modified the manuscript; and MTQ designed the manuscript and approved the final manuscript for publication. All authors read and approved the final manuscript.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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