



Molecular and therapeutic effects of mesenchymal stem cell-derived exosomes on autoimmune diseases

Fatma Sengul Bag, Omer Faruk Bag

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Fatma Sengul Bag, Department of Biochemistry, Adiyaman University Faculty of Pharmacy, Adiyaman 02040, Türkiye

Omer Faruk Bag, Adiyaman Training and Research Hospital, Adiyaman 02040, Türkiye

Corresponding author: Fatma Sengul Bag, PhD, Assistant Professor, Department of Biochemistry, Adiyaman University Faculty of Pharmacy, Central Classroom C Block, 3 Floor, Adiyaman 02040, Türkiye. fatmasengul245@gmail.com

Abstract

Autoimmune diseases are complex clinical conditions that present significant therapeutic challenges due to their intricate immunological mechanisms. Conventional treatment strategies, such as immunosuppressive drugs and anti-inflammatory therapies, often demonstrate limited efficacy and are associated with considerable side effects. Recently, mesenchymal stem cells (MSCs) have attracted growing interest as a promising therapeutic approach, owing to their immunomodulatory properties and ability to promote tissue repair. However, the direct application of MSCs faces several limitations, including the risk of immunogenicity and difficulties in large-scale production. In this context MSC-derived exosomes (MSC-Exos), nano-sized extracellular vesicles secreted by MSCs, have emerged as a compelling alternative to cell-based therapies. Enriched with proteins, lipids, and nucleic acids, these exosomes exhibit potent anti-inflammatory and immunomodulatory effects. Their primary mechanisms of action include enhancing the population of regulatory T cells, modulating macrophage polarization, and suppressing proinflammatory cytokines such as interleukin-6 and tumor necrosis factor- α . The therapeutic potential of MSC-Exos extends beyond individual conditions, encompassing a wide range of autoimmune diseases. For instance in Behçet's disease, they have been shown to regulate vasculitis and inflammatory processes by inhibiting proinflammatory cytokines and promoting endothelial cell regeneration. Moreover, MSC-Exos have demonstrated promising immunomodulatory effects in other autoimmune diseases, including systemic lupus erythematosus, rheumatoid arthritis, and multiple sclerosis. Through mechanisms such as inflammation suppression, vascular repair, and the restoration of immune homeostasis, MSC-Exos represent a versatile and innovative approach to autoimmune disease therapy. This review explored the molecular and therapeutic effects of MSCs and MSC-Exos in autoimmune diseases, with particular emphasis on their clinical potential in Behçet's disease, systemic lupus erythematosus, rheumatoid arthritis, and multiple sclerosis.

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Key Words: Mesenchymal stem cells; Exosomes; Autoimmune diseases; Immunomodulation; Behçet's disease; Systemic lupus erythematosus; Rheumatoid arthritis; Multiple sclerosis

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Core Tip: Autoimmune diseases result from dysregulated immune responses directed against self-antigens, leading to chronic inflammation and tissue damage. Mesenchymal stem cells (MSCs) and MSC-derived exosomes have demonstrated significant potential as therapeutic agents due to their strong immunomodulatory and regenerative properties. MSC-derived exosomes modulate immune responses by regulating cytokine secretion, suppressing inflammatory cell activity, and promoting immune tolerance. Their advantages, including low immunogenicity and the ability to cross biological barriers, make them a promising cell-free therapy for autoimmune. Even though preclinical and clinical findings are encouraging, further research is required to standardize protocols, optimize therapeutic efficacy, and ensure long-term safety.

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INTRODUCTION

Autoimmune diseases are a group of disorders resulting from an abnormal immune response against the body's own tissues. These conditions are particularly common in females, affect all age groups, and are typically characterized by the production of autoantibodies and the dysregulation of B cell and T cell activity[1,2]. Their pathophysiology is complex, involving interactions between genetic, environmental, and immunological factors[3]. Clinically, autoimmune diseases may be organ-specific or systemic and can present as inflammatory, neurological, gastrointestinal, or systemic conditions such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), type 1 diabetes, multiple sclerosis (MS), Behçet's disease (BD), psoriasis, and irritable bowel syndrome[4,5]. This overview specifically focused on RA, SLE, MS, and BD.

The molecular mechanisms underlying autoimmune diseases include the loss of autoantigen tolerance, cytokine dysregulation, molecular mimicry, and epitope spreading. The breakdown in tolerance of B and T cells to autoantigens leads to the production of autoantibodies, while specific variants of the human leukocyte antigen (HLA) genes are key in presenting these autoantigens. Elevated levels of proinflammatory cytokines and deficient anti-inflammatory cytokines contribute to chronic inflammation. Additionally, structural similarities between autoantigens and infectious agents can mislead the immune system into attacking healthy tissue, a phenomenon known as molecular mimicry. Epitope spreading refers to the expansion of the immune response from a single antigen to multiple autoantigens over time, further exacerbating disease progression. These processes are fundamental to the development and progression of autoimmune diseases[3].

Various therapeutic strategies aim to suppress abnormal immune responses and alleviate symptoms. Traditional treatments include corticosteroids and immunosuppressive drugs, but in recent years biological agents and targeted therapies have also been developed. In particular, tumor necrosis factor (TNF) inhibitors, therapies that target B cells, and agents that modulate cytokine signaling pathways have made significant advances in the treatment of autoimmune disease treatment. Regardless of all the advances, the treatment of autoimmune diseases still faces challenges, and a better understanding of the pathogenesis of these diseases requires the development of new and more effective therapeutic approaches. In this context mesenchymal stem cells (MSCs) are emerging as one of the most promising cellular therapies in the treatment of autoimmune diseases due to their immunomodulatory and regenerative properties[6].

MSCs were first isolated from bone marrow (BM) in the 1960s and 1970s and are defined as non-hematopoietic, multipotent cells capable of self-renewal and differentiation into various lineages[7]. They are present in multiple tissues, including BM, placenta, adipose tissue (AD), Wharton's jelly, umbilical cord (UC), and teeth[8]. According to the International Society for Cellular Therapy, MSCs must adhere to plastic surfaces, express specific surface markers (positive for CD73, CD90, and CD105; negative for CD45, CD34, CD14, CD11b, CD79a, CD19, and HLA-DR), and differentiate into mesodermal cell types under *in vitro* conditions[9]. Beyond their differentiation potential, MSCs have immunomodulatory properties, enabling them to modulate both innate and adaptive immune responses[10]. Research has shown that MSCs can suppress the activation, proliferation, and differentiation of natural killer (NK) cells, dendritic cells (DCs), macrophages, and B and T lymphocytes[11]. Their therapeutic effects are largely mediated by paracrine factors and exosomes, small extracellular vesicles that regulate inflammation, reprogram immune cells, and support tissue repair *via* their rich cargo of immunoregulatory molecules[12]. MSC-derived exosomes (MSC-Exos) offer advantages over whole-cell MSC therapies, including lower immunogenicity, the ability to cross the blood-brain barrier, no risk of unwanted differentiation, and the capacity to regulate inflammation through multiple mechanisms[13,14].

Extracellular vesicles are classified based on their biogenesis and size into exosomes, microvesicles, and apoptotic bodies (Figure 1)[15]. Exosomes (about 30-150 nm) originate from endosomes and are released when multivesicular bodies fuse with the plasma membrane[16]. They are formed *via* both the endosomal sorting complex required for transport-dependent pathway and the endosomal sorting complex required for transport-independent pathway. Initially thought to be cellular waste products, exosomes are now known to play essential roles in intercellular communication and immune regulation[17,18].

Exosomes are secreted by both hematopoietic (*e.g.*, reticulocytes, B and T lymphocytes, platelets, mast cells, DCs, macrophages) and non-hematopoietic cells (*e.g.*, epithelial cells, Schwann cells, astrocytes, neurons, melanocytes, mesothelial cells, adipocytes, fibroblasts, and tumor cells)[19]. They are present in biological fluids such as plasma, urine, cerebrospinal fluid, saliva, and breast milk. Their cargo [proteins, lipids, mRNAs, microRNAs (miRNAs), and DNA] reflects the physiological state of the parent cell and contributes to immune regulation, metabolism, and pathological processes (Figure 1)[20]. Exosome isolation methods include centrifugation, chromatography, polymer-based precipitation, and immunological techniques. Characterization is typically performed using nanoparticle tracking analysis, flow cytometry, electron microscopy, and western blotting[21,22]. Recent advances in high-throughput analysis of exosome content have led to the creation of dedicated databases such as ExoCarta, Vesiclepedia, and EVpedia[23-25].

IMMUNOMODULATORY EFFECT OF MSCS/MSC-EXOS

The immunosuppressive effect of MSCs is one of the key mechanisms underlying their immunotherapeutic potential. MSCs secrete various immunomodulatory factors to suppress the immune response and prevent autoimmune attacks in cases of excessive inflammation. These cells regulate the inflammatory response by secreting immunosuppressive mediators such as prostaglandin E2 (PGE2), indoleamine 2,3-dioxygenase (IDO), nitric oxide, transforming growth factor-beta (TGF- β), hepatocyte growth factor, interleukin-10 (IL-10), CD39, CD73, and programmed cell death ligands (PD-L1, PD-L2). The immunomodulatory effects of MSCs on immune cells are mediated through direct cell-to-cell interactions and the suppression of proinflammatory cytokine production *via* extracellular vesicles.

Notably, MSCs possess the ability to recognize danger signals and modulate immune responses through toll-like receptors (TLRs), enhancing their therapeutic potential[26]. MSC-derived extracellular vesicles contain various miRNAs, proteins, and lipids that regulate the immune response and exert anti-inflammatory effects. While miRNAs such as let-7b, miR-146a, miR-181c and miR-122 reduce inflammation by inhibiting the polarization of proinflammatory macrophage (M1), miR-21, miR-146a, miR-182 and miR-223 modulate the immune response by regulating TLR signaling pathways[27-29]. While miR-125a and miR-99b regulate TLR-4 signaling, miR-182 can affect MSC differentiation by decreasing TLR-4 expression[30,31]. In addition, miR-17 inhibits the release of proinflammatory mediators by suppressing the activation of the NOD-like receptor protein-3 inflammasome[32].

MSC-derived extracellular vesicles reduce IL-1 β production by suppressing the activation of nuclear factor kappa B (NF- κ B) with their protein contents such as TGF- β and PGE2, and they calm inflammation[33,34]. These vesicles suppress the activation of T and B cells by acting directly on immune cell activity, support tissue regeneration by increasing the proportion of anti-inflammatory macrophage (M2), and reduce mast cell activity[35,36]. While M1 macrophages secrete proinflammatory cytokines such as TNF- α and IL-1 β , M2 macrophages produce immunosuppressive factors such as IL-10. MSC-Exos increase the expression of IL-10 and simultaneously decrease the levels of vascular endothelial growth factor (VEGF)-A, interferon-gamma (IFN- γ), IL-12, and TNF- α by promoting the conversion of M1 to M2[6].

Vasandan *et al*[37] showed that human MSCs modulate the immune response by modulating the metabolic phenotype of macrophages through PGE2. PGE2 secreted by MSCs promotes the conversion of macrophages from a proinflammatory (M1) to an anti-inflammatory (M2) phenotype by promoting the transition from glycolysis to oxidative phosphorylation[37]. This mechanism underscores the crucial role of MSC-Exos in modulating immune cells and demonstrates that it has therapeutic potential for regulating inflammation.

Moreover, MSC-derived extracellular vesicles carry anti-inflammatory proteins such as TNF-stimulated gene 6 and cyclooxygenase-2, inhibit the migration of polymorphonuclear granulocytes into tissues, and regulate the inflammatory immune response[38,39]. The C-C motif chemokine receptor 2 in their membrane structure inhibits inflammatory macrophage functions by interacting with monocyte chemoattractant protein 1[27,40].

MSC-Exos suppress the proliferation and differentiation of B cells and the secretion of immunoglobulins in a dose-dependent manner. CD19⁺/CD86⁺ inhibit activated B cells and promote IL-10-producing regulatory B cells. They also decrease B cell activity by inhibiting the phosphatidylinositol 3-kinase/protein kinase B signaling pathway *via* miR-155-5p and increasing the expression of genes involved in immune regulation[6].

One of the mechanisms of MSC-Exos is to prevent the progression of autoimmune diseases by suppressing the proliferation and activation of T cells and restoring immune homeostasis. MSC-Exos, which carry immunosuppressive molecules such as TGF- β , IDO protein, and miR-125a-3p, regulate the T helper 1/2 (Th1/Th2) balance, promote regulatory T cell (Treg) differentiation, and suppress inflammatory responses. While adenosine inhibits T cells through its signaling effect, IL-1 β -stimulated MSC-Exos induce apoptosis of T cells by increasing PD-L1 and TGF- β expression and increasing the proportion of Treg cells.

In experimental autoimmune encephalomyelitis (EAE) and colitis models, MSC-Exos have been shown to suppress CD4⁺ T cell proliferation, decrease IL-17 and IFN- γ production, and stabilize inflammation by increasing TGF- β and IL-10 levels. In addition, it indirectly supports Treg cell formation by directing monocytes into the M2 macrophage phenotype and suppresses autoimmune responses by increasing immune tolerance[6,41].

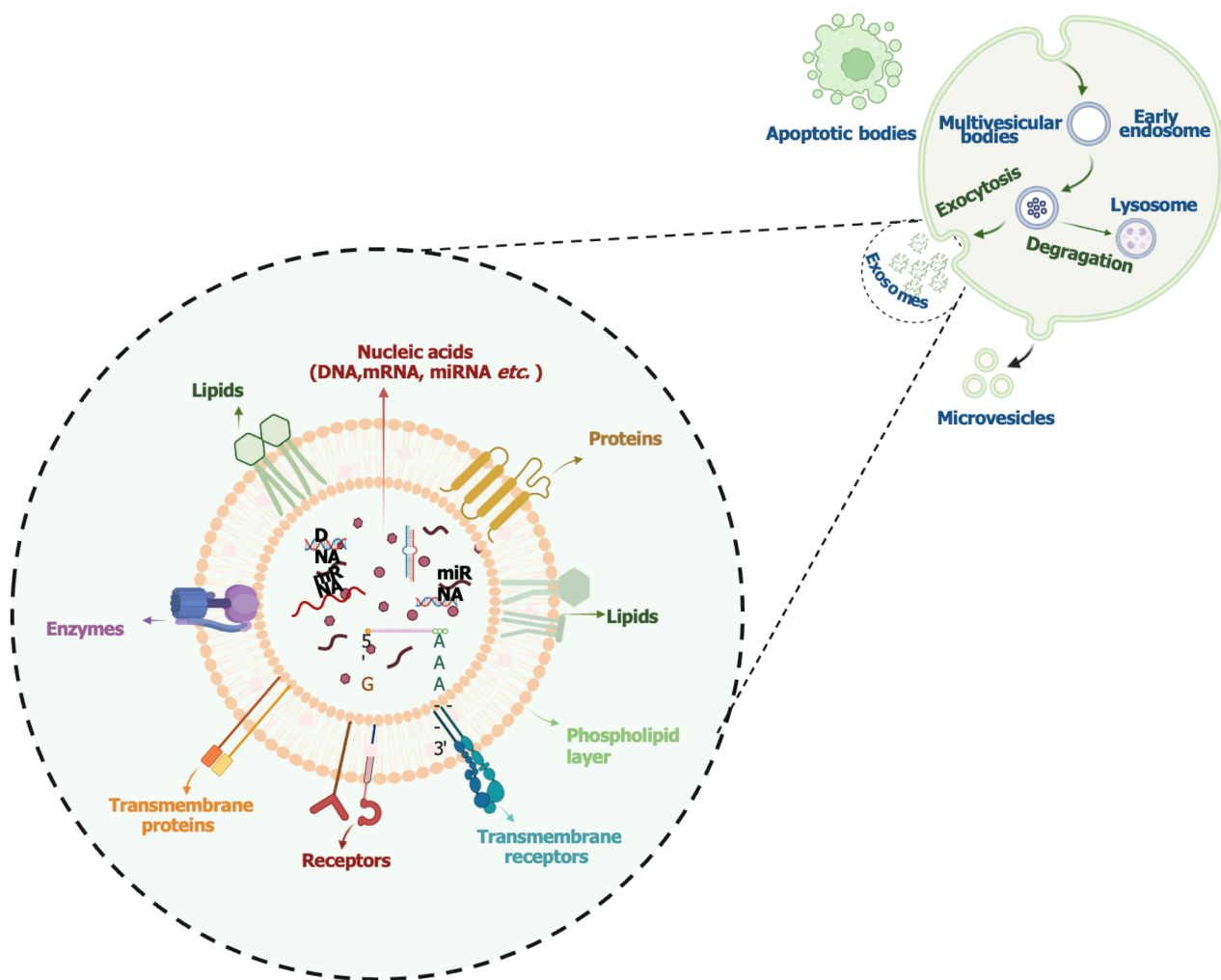


Figure 1 Biogenesis and composition of exosomes. Created with BioRender.com. miRNA: MicroRNA.

The ability of MSC-Exos to regulate the immune response is also mediated by NF- κ B-mediated, MyD88-dependent mechanisms. These exosomes suppress proinflammatory cytokine levels while increasing the expression of IL-10 and TGF- β 1. Monocytes interacting with exosomes contribute to immune tolerance by directing CD4⁺ T cells to the Treg phenotype. In animal models, MSC-Exos have been shown to prolong the survival of allogeneic skin grafts and regulate the immune response[42]. These mechanisms explain the immunosuppressive effect of MSC-Exos and reveal their therapeutic potential in autoimmune diseases and inflammatory processes.

THERAPEUTIC POTENTIAL OF MSCS/MSC-EXOS IN AUTOIMMUNE DISEASES

BD

BD is a relapsing autoinflammatory disorder with a broad clinical spectrum that includes oral and genital ulceration, skin lesions, uveitis, and vascular involvement[5]. Although the etiopathogenesis of the disease is not yet fully understood, it is believed that HLA-B51-related genetic predisposition, epigenetic alterations, environmental factors, and infectious agents trigger the immune system and lead to an increase in proinflammatory cytokines[43,44]. The disruption of the Th1/Th2 balance, the proliferation of Th17 cells, and the dysregulation of Treg cell functions play an important role in immunopathogenesis[45,46]. This process is characterized by an overactivation of the innate and adaptive immune system.

The interaction between major histocompatibility complex-II and the T cell receptor promotes Th1 cell differentiation (IFN- γ , TNF- α , IL-12) *via* antigen-presenting cells, IL-12, and IL-2 and Th17 cell differentiation (IL-17, TNF- α , IL-22) *via* TGF- β , IL-6, and IL-1 β . Th2 (IL-4, IL-6, IL-10) cells play a limited role, while loss of function of IL-2 and IL-12-dependent Treg cells causes uncontrolled progression of inflammation[47-49]. Macrophages exacerbate inflammation by switching to the M1 phenotype (TNF- α , IL-6, IL-8) under the influence of IFN- γ and granulocyte-macrophage colony-stimulating factor, while IL-4, IL-13, and macrophage colony-stimulating factor-mediated M2 (IL-10) are suppressed. Gamma delta T and NK cells (IFN- γ , TNF- α) increase Th1/Th17 activity. Neutrophils (IFN- γ , IL-8, granulocyte-macrophage colony-stimulating factor) are overactivated and lead to oxidative stress, endothelial dysfunction, thrombosis, and vasculitis,

which exacerbates the mucocutaneous lesions and inflammatory damage[48,49] (Figure 2).

Currently, various drugs such as colchicine, corticosteroids, immunosuppressants (azathioprine, cyclophosphamide), IFN, and anti-TNF biologics (infliximab, adalimumab, etanercept) are used to treat BD[50]. However, current treatments generally only alleviate symptoms, many patients develop resistance, and the need for more effective, less toxic new treatment options is increasing, especially in cases of severe organ involvement[47]. MSCs and their exosomes can suppress the autoimmune response by restoring the functions of Treg cells[51]. Considering the dysregulation of the innate immune response and the abnormalities in the adaptive immune system in the pathogenesis of BD, MSC-Exos could suppress the autoinflammatory process and alleviate the clinical symptoms by regulating the phenotype of immune cells[49]. In addition, it can suppress the activation of Th1 and Th17 cells and reduce inflammation by promoting the immunosuppressive functions of Treg cells[52].

In the study conducted by Mazaheri *et al*[47] in C57BL/6 mice in which herpes simplex virus type 1 was used as a model for BD, intraperitoneal MSCs were administered at different time points (before, simultaneously, and after herpes simplex virus type 1 infection). MSCs decreased the production of proinflammatory cytokines by suppressing TNF- α , IFN- γ , and IL-17 expression and regulated the immune response by inhibiting DC maturation and T cell, B cell, and NK cell activity. The results showed that MSCs slow disease progression by suppressing inflammation and have therapeutic potential[47].

In this context MSC-Exos have the potential as a novel therapeutic approach for patients resistant to conventional therapies in the treatment of BD. In a clinical case report, leg ulcers associated with BD that were resistant to conventional therapies were successfully healed by treatment with MSCs. A 55-year-old patient with recurrent oral and genital ulcers, papulopustular lesions, and walking disability was diagnosed with BD due to recurrent leg ulcers. Previously, conventional immunosuppressive therapy and anti-TNF agents (adalimumab, etanercept) were administered, but no clinical improvement was achieved. The patient received MSC injections in combination with low-dose prednisone and thalidomide. After treatment complete healing of ulcers was observed on one leg and significant improvement on the other leg. During the follow-up period, remission of the lesions and preservation of leg function was reported for 34 months. The results suggest that MSC infusion could be a safe and effective therapeutic option for the treatment of refractory leg ulcers due to BD[53].

BD-associated uveitis (BU) is characterized by severe inflammation that can lead to permanent vision loss and is refractory in some patients despite current immunosuppressive therapies[54]. Therefore, the need for new immunomodulatory treatment approaches is increasing. To investigate the therapeutic effect of MSC-Exos on experimental autoimmune uveitis (EAU), Bai *et al*[55] established an EAU model in rats immunized with the peptide interphotoreceptor retinol-binding protein 1177-1191 and administered periocular MSC-Exos injections for 7 days after disease onset. After treatment, a significant decrease in the severity of EAU was observed, and T cell subsets and inflammatory cell infiltration in ocular tissues were suppressed. MSC-Exos inhibited the chemotactic effects of C-C motif chemokine ligand 2 and C-C motif chemokine ligand 21 on inflammatory cells and thus reduced the migration of immune cells into the eye. However, no direct inhibitory effect on interphotoreceptor retinol-binding protein-specific T cell proliferation was observed[55]. These results suggest that MSC-Exos alleviates the severity of EAU by regulating inflammation and protects ocular tissue by reducing immune cell infiltration. Since BU results from similar immune mechanisms, this study suggests that MSC-Exos could be considered as a potential immunomodulatory agent for the treatment of BU.

In a study published in the preprint, the immunomodulatory effect of exosomes derived from AD-derived MSCs, specifically IFN- γ -pre-stimulated exosomes (IFN + Exo), on BU was investigated. Peripheral blood mononuclear cells from patients with BU and healthy individuals were cultured with exosomes, and their effects on lymphocyte proliferation, cell viability, and apoptosis were evaluated. IFN + Exo increased apoptosis of T lymphocytes in patients with BU, suppressed proinflammatory cytokines such as IL-17 and TGF- β , and stabilized the immune response by increasing IL-10 expression. These effects have been shown to be mediated by the induction of apoptosis *via* the Fas/FasL signaling pathway and the suppression of proinflammatory cytokines. The results suggest that IFN + Exo can be used as a potential therapeutic agent by controlling inflammation in patients with BU[56].

Intravitreal BM-MSCs (1.8×10^6 cells) were injected in 3 patients with advanced retinal vasculitis due to BU and severe vision loss unresponsive to conventional immunosuppressive therapies. However, no significant improvement in visual acuity was achieved during the 12-month follow-up period. However, it was observed that MSC treatment partially modulated the inflammatory response[57]. The results suggest that MSCs are not sufficient to reverse vision loss in advanced retinal vasculitis but that they have the potential to suppress inflammation.

Although studies related to BD are limited, the fact that MSC-Exos suppress IL-17 and TGF- β levels, regulate Th1/Th17 cell balance, and reduce inflammatory cell infiltration[6] can be considered a promising approach for the treatment of BD. Further clinical studies on the efficacy and long-term effects of MSC-Exos in different phenotypes of BD are needed. Figure 2 summarizes the immunopathogenesis of BD and potential therapeutic effects of MSCs/MS-Exos.

SLE

SLE is a chronic autoimmune disease characterized by a dysregulation of the immune system leading to the production of autoantibodies (such as anti-double-stranded DNA and antinuclear antibodies) and subsequent inflammation affecting multiple organ systems[58]. This immunological imbalance is due to the presence of autoreactive T and B lymphocytes, leading to polyclonal activation of B cells and excessive production of autoantibodies and proinflammatory cytokines by plasma cells[59].

The pathogenesis of SLE is complex and multifactorial. It includes a genetic predisposition, environmental factors, and hormonal influences, which together contribute to impaired immune tolerance and activation of autoreactive T and B cells[60]. One of the most important clinical manifestations of SLE is lupus nephritis, which occurs in about 40%-60% of patients and can lead to end-stage renal disease if not treated effectively[61]. Treatment is usually with corticosteroids,

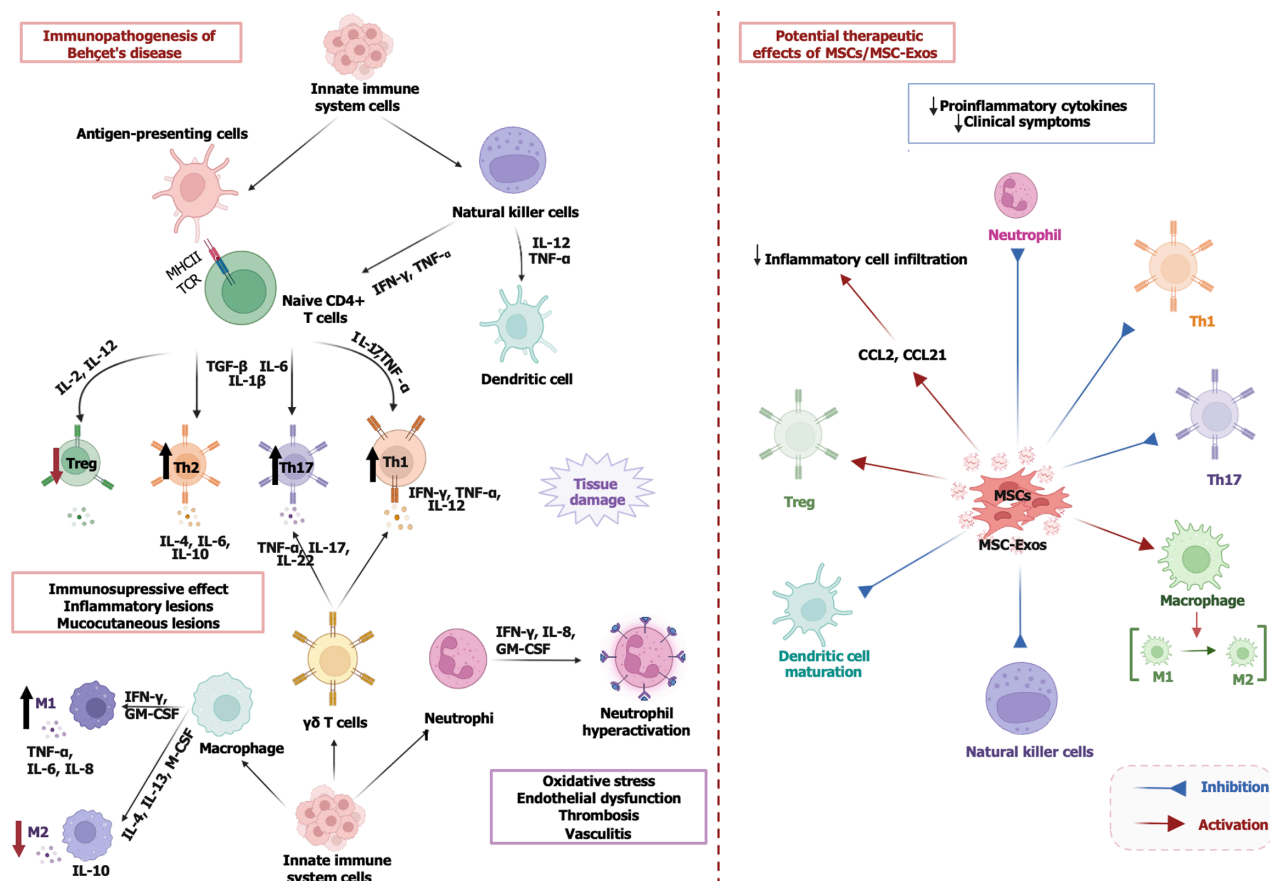


Figure 2 Immunopathogenesis of Behçet's disease and potential therapeutic effects of mesenchymal stem cells/mesenchymal stem cell-derived exosomes. Created with BioRender.com. MSCs: Mesenchymal stem cells; MSC-Exos: Mesenchymal stem cell-derived exosomes; MHC-II: Major histocompatibility complex class II; TCR: T cell receptor; IFN-γ: Interferon-gamma; TNF-α: Tumor necrosis factor-alpha; IL-12: Interleukin-12; Treg: Regulatory T cell; Th1: T helper 1; Th17: T helper 17; TGF-β: Transforming growth factor-beta; GM-CSF: Granulocyte-macrophage colony-stimulating factor; M-CSF: Macrophage colony-stimulating factor; γδ T cells: Gamma delta T cells; M1: Proinflammatory macrophage; M2: Anti-inflammatory macrophage; CCL2: C-C motif chemokine ligand 2; CCL21: C-C motif chemokine ligand 21; miRNA: MicroRNA.

nonsteroidal anti-inflammatory drugs, and immunosuppressants (cyclophosphamide, mycophenolate mofetil, azathioprine, and leflunomide); intravenous (IV) immunoglobulin is rarely preferred. However, more than one-third of patients show resistance to these therapies or relapse[62,63], contributing to the need for new treatment strategies.

Recent studies have shown that MSCs can improve clinical outcomes in patients with SLE, especially in cases of refractory lupus nephritis[64]. This therapeutic efficacy of MSCs is largely regulated by paracrine factors, while their immunoregulatory activity has been shown to be mainly mediated by MSC-Exos[65]. For example, Liu *et al*[66] emphasized the potential of MSC-Exos to deliver miRNAs and other bioactive molecules that can regulate immune responses and promote tissue repair. Dou *et al*[67] demonstrated that tsRNA-21109 contained in MSC-Exos inhibited the conversion of macrophages to the proinflammatory M1 phenotype, thereby reducing inflammation and thus alleviating SLE symptoms.

The therapeutic effects of MSCs in SLE are mediated by different mechanisms. Geng *et al*[68] demonstrated that reduced Let-7f levels in BM-derived MSCs contribute to the Th17/Treg imbalance observed in patients with SLE, suggesting that MSCs may play a role in restoring immune homeostasis. AD-derived MSCs treatment suppressed autoimmunity by increasing IL-10-producing regulatory B cells, decreasing proinflammatory cytokine levels, increasing the proportion of Treg cells, and decreasing autoantibody production and tissue damage[69].

In a study conducted by Wang *et al*[70] in patients with active and refractory SLE, transplantation of UC-derived MSC was shown to significantly improve immune tolerance and clinical parameters by regulating T and B cells, suppressing the production of proinflammatory cytokines and increasing Treg cells, with a low side effect profile. Furthermore, in patients with severe and drug-resistant SLE, allogeneic transplantation of BM and/or UC-derived MSCs restored the balance of the immune system by increasing Treg cells and modulating the autoimmune response, while decreasing disease activity and improving renal function[71]. The 5-year overall survival rate was reported to be 84%[70]. Some representative clinical studies are listed in Table 1.

MSC-Exos have been shown to have anti-inflammatory properties and can inhibit the proliferation of autoreactive B cells, which play a central role in the pathogenesis of SLE. Ng *et al*[72] reported that MSCs can inhibit B cell proliferation and antibody production through T cell-mediated mechanisms (suppression of Th1/Th2/Th17 populations and increase in Treg cells), highlighting the importance of MSCs in regulating humoral immunity in SLE. This is particularly important given the role of autoantibodies in disease progression and associated organ damage.

Table 1 Clinical trials (completed and ongoing) investigating mesenchymal stem cell-based therapies in autoimmune diseases

Study type	MSC source	Disease	Patients (treatment/control)	Administration	Follow-up (months)	Mechanism of action	Outcome measures	Conclusion	Trial registration number	Ref.
-	BM-MSCs (autologous)	SLE	2 (2/0)	1×10^6 cells/kg, IV infusion	4	Immunomodulation	Safety and efficacy, Sclera SLEDAI and BILAG scores	CD4 ⁺ CD25 ⁺ FoxP3 ⁺ cells increased, but the disease did not show remission		[121]
Phase I/II	UC-MSCs (allogeneic)	SLE	244 (21 ¹ /78)	1×10^6 cells/kg, IV infusion	6	FLT3 L production, CD1c ⁺ DC proliferation, IFN- γ effect	Clinical improvement, CD1c ⁺ DC and FLT3 L levels	Increased FLT3 L levels and increased number of tolerant CD1c ⁺ DCs, suppression of inflammation	NCT01741857	[122]
Phase II	BM-MSCs	SLE	3 (3/0)	9×10^7 cells/kg, IV infusion	9	Immunomodulation	SLEDAI, proteinuria values, renal function	Significant reduction in disease activity and improvement in kidney function		[123]
-	UC-MSCs, BM-MSCs	Persistently active SLE	87 (87/0)	1×10^6 cells/kg, IV infusion	48	Suppression of the proliferation of T and B lymphocytes, modulation of the inflammatory reaction and proliferation of Treg cells	Sclera SLEDAI, ANA, dsDNA, clinical remission, relapse, and survival rate	Prolonged clinical remission and improvement in organ function		[124]
Phase I	AD-MSCs (allogeneic)	Refractory lupus nephritis	9 (9/0)	2×10^6 cells/kg, IV infusion	12	Immunomodulation	SLEDAI, 24-h urinary protein excretion, serum creatinine, anti-dsDNA antibodies	Effective in reducing urinary protein excretion and disease activity in the short term, single dose limited for long-term remission		[125]
-	UC-MSCs	Lupus nephritis	37 (17/20)	3×10^7 cells/kg, IV infusion	12	Immunomodulation	SLEDAI, ANA, dsDNA urinary protein excretion, safety, and tolerability	Reduction of disease activity, regulation of the balance of inflammatory cytokines, improvement of serological markers and renal function		[126]
Phase I/II	BM-MSCs (autologous)	RA with knee involvement	30 (15/15)	Intra-articular implantation of 40 million autologous BM-MSCs per knee joint	12	Immunomodulation, suppression of inflammatory cytokines	WOMAC, VAS, time to gelling, pain-free walking distance, standing time	Safe and well tolerated, with a trend towards clinical efficacy with improvements in WOMAC, VAS, gelling time, and pain-free walking distance	NCT01873625	[127]
Phase I/II	UC-MSCs	RA	63 (32 MSC monotherapy group, 31 MSC + IFN- γ group)	UC-MSC transplantation, with some patients receiving	3	IFN- γ enhanced MSC therapeutic efficacy	EULAR response rates, ACR20 response rates	The combination therapy of MSC and IFN- γ improved RA outcomes	ChiCTR-INR-17012462	[128]

				recombinant human IFN- γ 1×10^6 cells/kg 1 dose				with an ACR20 response of 93.3% at 3 months <i>vs</i> 53.3% with MSC alone, with no major safety concerns at 1 year		
Phase I/IIa	AD-MSCs (autologous)	DMARD- resistant RA	54 (39 ² /15)	2.0 or 2.86×10^6 cells/kg, IV infusion	12	Immunomodulation	RAPID3, DAS28, and ACR20	Study ongoing	NCT04170426	
Phase I/II	UC-MSCs	RA	172 (136/36)	IV infusion of 4×10^7 UC-MSCs in combination with DMARDs	Follow-up examinations after 3, 6, and 8 months	Immunomodulation, suppression of inflam- matory cytokines	ACR improvement criteria, DAS28, HAQ, TNF- α , IL-6 levels, CD4 ⁺ CD25 ⁺ FoxP3 ⁺ Treg percentage	Safe, TNF- α and IL-6 levels decreased, the proportion of Tregs increased, and a clinical improvement was observed. The therapeutic effect lasted 3-6 months and repeated infusions increased the efficacy	NCT01547091	[89]
Phase I/II	MSCs (allogeneic)	RA	30 (15/15)	Dose not specified IV infusion	1	Immunomodulation, suppression of inflam- matory response	Safety, tolerability, preliminary efficacy, DAS28	Study ongoing; results not yet published	NCT05925647	
Phase I	UC-MSCs (allogeneic) (BX- U001)	RA	16 (8/8)	$(0.75-1.5) \times 10^6$ cells/kg, 24 BX-U001 IV infusion	24	Immunomodulation and anti-inflammatory effect	Safety and tolerability, ACR20, HAQ, DAS28, CRP, ESR, SDAI, anti-CCP	Study ongoing	NCT03828344	
Phase I/II	UC-MSCs (allogeneic)	RA	105 (52/53)	1×10^6 cells/kg, IV infusion	12	Immunomodulation, regulation of Treg/Th17 balance, suppression of inflammatory cytokines	DAS28, HAQ, serum cytokine levels (IFN- γ , IL-10, IL-6), Treg/Th17 ratio	Safe and effective, clinical improvement persisted for 48 weeks, and high IFN- γ levels correlated with better treatment response	ChiCTR-ONC- 16008770	[129]
Phase Ib/IIa	AD-MSCs (allogeneic) (Cx611)	Refractory RA	53 (46/7)	1, 2 or 4×10^6 /kg, IV infusion	6	Immunomodulation, suppression of inflam- matory response	Safety, tolerability, pre-activity	Well tolerated, with no dose-dependent toxicity observed. A trend towards clinical efficacy was observed	NCT01663116	[130]
Phase Ia	UC-MSCs	RA	9 (9/0)	2.5, 5.0 or 10.0×10^7 cells/patient, IV infusion	1	Immunomodulation	Safety, DAS28, ESR, and CRP levels	Significant decrease in DAS28 score at week 4, decrease in ESR and CRP values	NCT02221258	[131]
Phase I	BM-MSCs (autologous)	RA	9 (9/0)	1×10^6 cells/kg, IV injection	12	Immunomodulation	DAS28-ESR, VAS, and ESR	Significant reduction in DAS28-ESR, VAS, and ESR	NCT03333681	[132]
Phase I	Placenta derived MSCs (allogeneic)	SPMS	5 (5/0)	3×10^6 cells/kg, IV injection	6	Immunomodulation	EDSS, cytokines, DTI, fMRI, cognitive and psychological	Results not yet published	NCT06360861	

								evaluations		
Phase I/II	MSCs (autologous)	MS	24 (24/0)	1 × 10 ⁶ cells/kg, IV or intrathecal injection	48	Immunomodulation	EDSS, adverse events	Results not yet published	NCT04823000	
Phase I	BM-MSCs (autologous)	MS	7 (7/0)	(1-2) × 10 ⁶ cells/kg, IV infusion	12	Immunomodulation	EDSS, MRI, adverse events	Results not yet published	NCT03778333	
Phase II	BM-MSCs (autologous)	MS	48 (32/16)	1 × 10 ⁶ cells/kg, IV or intrathecal injection	12	Immunomodulation	EDSS, MRI, ambulation score, relapse rate	Results not yet published	NCT02166021	
Phase I/II	UC-MSCs (allogeneic)	MS	20 (20/0)	Dose not specified IV injection	12	Immunomodulation	EDSS, NRS, PASAT, the nine-hole peg test, and 25-foot walking time. Short-form 36	Results not yet published	NCT02034188	

¹A total of 166 patients with systemic lupus erythematosus were included in the study. There were 21 patients with systemic lupus erythematosus who did not respond to conventional treatment and were treated. ²Nine subjects in phase 1 and 30 subjects in phase IIa. MSC: Mesenchymal stem cell; BM-MSCs: Bone marrow derived mesenchymal stem cells; SLE: Systemic lupus erythematosus; IV: Intravenous; SLEDAI: Systemic lupus erythematosus disease activity index; BILAG: British Isles lupus assessment group; UC-MSCs: Umbilical cord derived mesenchymal stem cells; FLT3 L: FMS-like tyrosine kinase 3 ligand; DC: Dendritic cells; IFN-γ: Interferon-gamma; ANA: Antinuclear antibody; dsDNA: Double-stranded DNA; AD-MSCs: Adipose tissue derived mesenchymal stem cells; RA: Rheumatoid arthritis; WOMAC: Western Ontario and McMaster Universities Arthritis Index; VAS: Visual analogue scale; EULAR: European Alliance of Associations for Rheumatology; ACR20: American College of Rheumatology 20; DMARD: Disease-modifying antirheumatic drug; RAPID3: Routine assessment of patient index data 3; DAS28: 28-joint Disease activity score; HAQ: Health Assessment Questionnaire; TNF-α: Tumor necrosis factor-alpha; IL-6: Interleukin-6; Treg: Regulatory T cell; CRP: C-reactive protein; ESR: Erythrocyte sediment rate; SDAI: Simplified Disease Activity Index; anti-CCP: Anti-cyclic citrullinated peptide; SPMS: Secondary progressive multiple sclerosis; MS: Multiple sclerosis; EDSS: Expanded Disability Status Scale; DTI: Diffusion tensor imaging; fMRI: Functional magnetic resonance imaging; MRI: Magnetic resonance imaging; NRS: Neurological rating scale; PASAT: Paced auditory serial addition test; Th: T helper cell.

Despite the promising results there are still some challenges in the clinical application of MSC therapies in SLE. The variability in the origin and preparation of MSCs may affect their therapeutic efficacy, and further research is needed to standardize protocols for the isolation and characterization of MSCs[73,74]. It is important that SLE is not recognized today as a uniform disease but as a heterogeneous spectrum of clinical phenotypes with different immunopathological courses. This phenotypic diversity poses a major challenge to standard treatment protocols and underscores the need for personalized medical approaches in the treatment of the disease[75].

MSC-Exos may offer phenotype-specific therapeutic benefits due to various immunoregulatory molecules such as miRNAs and tRNA fragments. Therefore, it is recommended that future clinical trials stratify patients according to their disease phenotype to further evaluate the efficacy of MSC-Exos treatment and tailor treatment strategies to individual immune profiles. This approach could significantly help to improve clinical outcomes and reduce treatment resistance in SLE.

RA

RA is a chronic, systemic, autoimmune, inflammatory disease that mainly affects the synovial joints and is associated with genetic and environmental factors although its etiology is not yet fully understood[76]. Epidemiologic data show that RA occurs in 0.5%-1.0% of the adult population and can affect any age group although it is more common in females and the elderly[77]. Synovial hyperplasia, cell activation, joint inflammation, and the invasion of synovial tissue into adjacent bone and cartilage are characteristic of RA[77]. Many different cell types such as macrophages, DCs, B lymphocytes, T lymphocytes, chondrocytes, fibroblasts, and osteoclasts are involved in the pathophysiology. Macro-

phages trigger cartilage destruction, joint erosion, and fibroblast proliferation by producing proinflammatory cytokines and enzymes that maintain inflammation in RA[78], while B lymphocytes promote T cell activation through their autoreactive forms by increasing the production of autoantibodies (rheumatoid factor and anti-cyclic citrullinated peptide) and triggering the release of proinflammatory cytokines, leading to tissue damage[79]. CD4⁺ T cells activate the phosphatidylinositol 3-kinase signaling pathway by interacting with major histocompatibility complex class II and trigger the inflammatory response by stimulating CD8⁺ T cells[80,81]. Th1 and Th17 cells promote osteoclastogenesis, pannus formation, and synovial neoangiogenesis by secreting IFN- γ , TNF- α , and IL-17, while Th2 cells regulate B cell activation by secreting IL-4 and IL-5[82]. **Figure 3** illustrates immunopathogenesis.

In RA fibroblast-like synoviocytes (FLS) initiate inflammatory and destructive processes in the joint and play an important role in cartilage damage[83]. Treatment includes synthetic disease-modifying antirheumatic drugs (DMARDs/methotrexate, leflunomide, sulfasalazine, hydroxychloroquine), biological DMARDs (anti-TNF drugs, tocilizumab, anakinra, abatacept, rituximab), and corticosteroids, which aim to improve disease progression by suppressing inflammation[84]. However, despite current advances many patients with RA do not respond to treatment and suffer from unwanted side effects[85].

MSCs have shown promise as a target for the treatment of RA as they can effectively regulate cartilage bone formation and immune response[86]. The first pilot study, published in 2011[87] investigated the safety and efficacy of autologous AD-derived MSCs in patients with RA. Four patients with RA received single, double, or quadruple dose IV infusions of 2×10^6 to 3.5×10^8 cells. Two patients also received an intra-articular injection. During a 13-month follow-up period, an improvement in the visual analog scale and Korean Western Ontario McMaster Score was observed. Multiple infusions increased efficacy, and up to 8×10^8 cells were shown to be safe. The study was considered the first demonstration of the safety of autologous MSC therapy in RA[87].

In patients with refractory RA, infusion of allogeneic MSCs from the BM and endometrium was reported to reduce erythrocyte sedimentation rate, improved the 28-joint Disease Activity Score, and reduced anti-cyclic citrullinated peptide levels although this clinical improvement was transient due to the short follow-up period[88]. A study in a larger group of patients showed that coadministration of allogeneic UC-derived MSCs with DMARDs increased CD4⁺ Treg cells and suppressed disease activity for up to 6 months, and repeated MSC infusions increased therapeutic efficacy[89]. *In vitro* UC-derived MSCs suppressed FLS proliferation and IL-6 secretion from patients with RA *via* IL-10, IDO, and TGF- β 1, induced T cell hyporesponsivity *via* PGE2, TGF- β 1, and nitric oxide, and increased CD4⁺FoxP3⁺Treg cells.

In a mouse model systemic infusion of UC-derived MSCs reduced the severity of arthritis, decreased proinflammatory cytokines, and regulated the Th1/Th2 balance by increasing IL-10 levels[90]. In another study IL-1 β -stimulated human UC-derived MSCs alleviated RA symptoms by inducing apoptosis of FLS[91]. BM-derived MSCs suppressed the production of TNF- α , IL-17, IL-6, IL-2, IFN- γ , and IL-9 in T cells from patients with RA, and this effect was observed in all T cell subsets. It also supported immune tolerance by increasing the mRNA expression of IL-10 and TGF- β [92].

UC-derived MSCs with increased TNF receptor 2 expression reduced joint inflammation and cartilage destruction by blocking TNF- α [93]. Orthotopic transplantation of BM-derived MSCs with microfracturing and thermal gel reduced joint inflammation by lowering the concentration of inflammatory cytokines[94]. Encapsulation of BM-derived MSCs in alginate hydrogel suppressed inflammation by inhibiting DCs[95]. MSCs with increased expression of CXC chemokine receptor 7 alleviated arthritis symptoms by suppressing inflammation, while BM-derived MSCs expressing IL-10 promoted articular cartilage repair by inhibiting inflammation[96,97]. Consistent with these findings, the immunomodulatory and anti-inflammatory effects of MSC-Exos in RA have been extensively studied. Other representative clinical studies in this field are summarized in **Table 1** (<http://www.clinicaltrials.gov/>).

Studies have reported that these exosomes can suppress the activation and proliferation of synovial FLS involved in RA pathology. For example, Su *et al*[98] showed that MSC-derived exosomal long non-coding RNA HAND2-AS1 suppressed FLS activation and proliferation *via* miR-143-3p/TNFAIP3/NF- κ B pathways, while reducing inflammation and inducing apoptosis[98]. Exosomal miRNA-320a derived from BM-derived MSC suppressed the expression of CXC motif chemokine ligand 9, a chemokine involved in inflammatory responses, and halted the progression of RA by reducing FLS activation and inflammatory response[86].

These exosomes also suppressed apoptosis and promoted FLS proliferation by inhibiting the NF- κ B signaling pathway *via* the expression of fibrinogen-like protein 1, thereby reducing RA-induced joint damage[99]. In addition, MSC exosomes containing miR-150-5p inhibited synoviocyte hyperplasia and angiogenesis by suppressing the expression of matrix metalloproteinase 14 and VEGF, thereby slowing RA progression[100]. MiR-21-containing exosomes have been shown to alleviate RA symptoms by regulating immune imbalance *via* the ten-eleven translocation protein 1/Kruppel-like factor 4 axis[101]. Exosomes from UC-derived MSCs inhibited the development of RA by exerting a regulatory effect on the balance of Th1/Th17 and Treg cells. MiRNA-140-3p from UC-derived MSC exosomes reduced joint damage by suppressing serum/glucocorticoid regulated kinase 1 expression[102]. Synovium-derived MSC-Exos suppressed signal transducer and activator of transcription 3 activity by targeting miR-485-3p *via* the circEDIL3 molecule and limited RA-induced angiogenesis by reducing VEGF levels[103]. MiR-146a-modified MSC-Exos have been shown to maintain immune balance by restoring the immunologic potential of MSCs[104].

MSC-derived exosomal circFBXW7 suppressed FLS proliferation, movement, and inflammation in RA. CircFBXW7 levels were low, miR-216a-3p levels were high, and histone deacetylation 4 levels were low in patients with RA. CircFBXW7, which is carried by MSC-Exos, bound miR-216a-3p, reduced its effect, and increased histone deacetylation 4 levels. This suppressed the excessive proliferation and inflammatory activity of FLS[105]. Meng *et al*[106] produced exosomes from MSCs overexpressing miRNA-124a and investigated the effects of these exosomes on RA-associated FLS cells. These exosomes inhibited the proliferation and migration of FLS cells and promoted their apoptosis. These results suggested that MSC-Exos are a suitable vector for the delivery of therapeutic miRNA-124a and may represent a novel strategy for the treatment of RA[106].

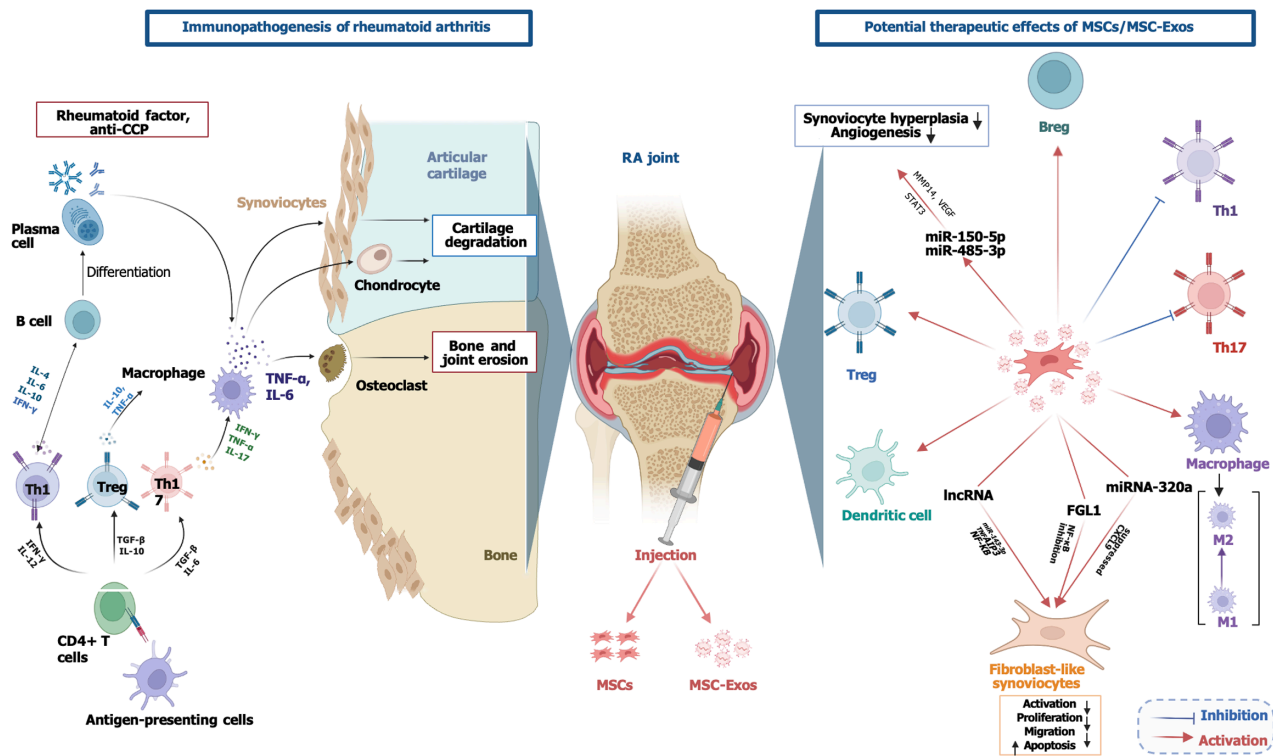


Figure 3 Immunopathogenesis of rheumatoid arthritis and therapeutic effects of mesenchymal stem cells/mesenchymal stem cell-derived exosomes. Created with BioRender.com. Anti-CCP: Anti-cyclic citrullinated peptide; RA: Rheumatoid arthritis; MSCs: Mesenchymal stem cells; MSC-Exos: Mesenchymal stem cell-derived exosomes; TNF- α : Tumor necrosis factor-alpha; IL-4: Interleukin-4; IFN- γ : Interferon gamma; Treg: Regulatory T cell; Th1: T helper 1; Th17: T helper 17; TGF- β : Transforming growth factor-beta; CD4 $^{+}$ T cells: Cluster of differentiation 4 positive T cells; Breg: Regulatory B cells; MMP14: Matrix metalloproteinase-14; VEGF: Vascular endothelial growth factor; STAT3: Signal transducer and activator of transcription 3; IncRNA: Long non-coding RNA; FGL1: Fibrinogen-like protein 1; NF- κ B: Nuclear factor kappa B; CXCL9: CXC motif chemokine ligand 9; M1: Pro-inflammatory macrophage; M2: Anti-inflammatory macrophage; miRNA: MicroRNA.

In a study on inhibition of bone and cartilage destruction, You *et al*[107] showed that dextran sulphate-modified MSC-Exos (DS-EXOs) have an anti-inflammatory effect in the treatment of RA by regulating macrophage heterogeneity. DS-EXOs accumulated in inflamed joints after systemic administration, converted M1 macrophages to an M2 phenotype, decreased TNF- α and IL-6 levels, and increased IL-10 production. It also provided an immunomodulatory effect in the synovial microenvironment by promoting the activation of Treg cells and suppressing the autoimmune response by inhibiting Th17. In a collagen-induced arthritis model, DS-EXOs, which showed similar therapeutic efficacy at a 10-fold lower dose compared with naked exosomes, reduced joint damage[107]. Figure 3 summarizes the immunopathogenesis of RA and potential therapeutic effects of MSCs/MSC-Exos.

MS

MS is a chronic, progressive disease of the central nervous system characterized by degeneration of the myelin sheath, axonal damage, and neuroinflammation through autoimmune mechanisms. It occurs in three clinical forms. Relapsing-remitting MS, the most common form, progresses in relapses and complete/partial remissions and affects 85%-90% of patients. Over time, it progresses to secondary progressive MS, which occurs without remission in 50%-60% of cases. Primary progressive MS, on the other hand, is a form that occurs in 15% of patients and in which neurological function gradually deteriorates[108].

Th1 and Th17 cells cause demyelination by secreting IFN- γ , IL-17, TNF- α , and IL-1, while CD8 $^{+}$ T cells contribute to axonal damage. Autoimmune B cells drive the disease through antigen presentation, autoantibody production, and cytokine secretion[109]. To investigate the immune-mediated mechanisms of MS, the EAE model is used as the gold standard in preclinical studies[110]. MSC-derived microvesicles carry immunosuppressive molecules such as PD-L1, galectin-1, and TGF- β and through these mechanisms reduce disease activity in the EAE model[111]. In addition, MSC-Exos containing immunosuppressive cytokines (TGF- β , IL-10) and anti-inflammatory biomolecules (PGE2, miR-155, miR-146a, miR-181c, miR-17, miR-21) suppressed T cell proliferation and effector T cell activity through these factors. These mechanisms contribute to the attenuation of the inflammatory process in the central nervous system by reducing the activity of Th1 and Th17 cells[41].

Intranasal administration of MSC-Exos by Fathollahi *et al*[112] reduced disease severity, increased the ratio of CD25 $^{+}$ FoxP3 $^{+}$ Treg cells, and showed a significant immunomodulatory effect by increasing TGF- β levels. After administration of placental MSC-Exos, improvement of motor function, activation of oligodendrocyte progenitor cells, and increased myelin repair were observed[113]. In mice with EAE, human AD-derived MSCs and MSC-Exos have been shown to reduce disease severity, attenuate myelin damage, and suppress inflammatory responses[114]. BM-derived MSCs

promoted remyelination by promoting oligodendrocyte progenitor cell proliferation and reduced neuroinflammation by shifting the microglia/macrophage phenotype from M1 to anti-inflammatory M2. Exosomes promoted the maturation of oligodendrocytes by increasing myelin-associated miRNAs such as miR-219 and miR-338 and suppressed inflammation by inhibiting the NF- κ B/TLR4 signaling pathway[115].

The periodontal ligament stem cell-derived secretome inhibited NOD-like receptor protein-3 inflammasome activation, decreased the production of proinflammatory cytokines (IL-1 β , IL-18), increased the proportion of Treg cells, and suppressed Th1 and Th17 responses[116]. Riazifar *et al*[14] observed that IV injection of IFN γ -Exo decreased the clinical score, reduced demyelination, and suppressed neuroinflammation. It also increased the number of CD4⁺CD25⁺FoxP3⁺ Tregs in spinal cord tissue. *In vitro* studies have shown that IFN γ -Exo decreased the levels of proinflammatory Th1 and Th17 cytokines in peripheral blood mononuclear cells and increased IDO levels. In addition, exosomes have been shown to suppress inflammatory processes by regulating cellular immune responses and could potentially be used in the treatment of autoimmune diseases and central nervous system disorders[14]. Therefore, MSC-Exos are thought to have important therapeutic potential in the regulation of neuroinflammation and the treatment of autoimmune diseases.

In the study conducted by Li *et al*[117], an improvement in the Expanded Disability Status Scale scores, a reduction in relapse frequency and a shift in immune response from Th1 to Th2 were observed in patients receiving UC-derived MSC infusions at a dose of 4×10^6 cells/kg every 2 weeks for a total of 6 weeks. However, in a triple-blind, placebo-controlled, randomized phase I/II clinical trial, AD-derived MSC (1×10^6 or 4×10^6 cells/kg) were administered to patients with secondary progressive MS, and it was reported that MSC treatment was safe but did not provide significant clinical improvement during the 12-month follow-up period[118]. In another phase I/II branch group study (NCT03326505), intrathecally administered doses of UC-derived MSCs (group A: Two doses; group B: One dose), and secretomes of UC-derived MSCs were administered 3 months later. Significant clinical improvements were observed in group A, particularly positive changes in CD3⁺CD4⁺ T cells and neurocognitive function. Magnetic resonance imaging data demonstrated neuroprotective effects with reduced lesion burden and increased cortical thickness in group A, while analysis of gene expression revealed activation of anti-inflammatory mechanisms[119]. To date there are 23 clinical studies on MS, some of which are summarized in Table 1 (<http://www.clinicaltrials.gov/>). A systematic review and meta-analysis reported that 40.4% of patients with MS improved after MSC therapy, 32.8% remained stable, and 18.1% worsened. Common minor adverse events included headache and fever, with no major complications observed[120].

CONCLUSION

Current approaches to the treatment of autoimmune diseases are still inadequate, and long-term effective solutions are limited. In this review the immunomodulatory effects of MSC-Exos on immune cells and their potential in the treatment of autoimmune diseases were discussed. The results suggested that MSC-Exos hold promise as cell-free biological treatment options and may offer a novel therapeutic approach for autoimmune diseases. However, despite the promising potential of MSC-Exos therapies, the lack of standardized protocols, isolation methods, and dosages pose a major challenge. In addition, the source of MSCs used for exosome production (autologous or allogeneic) is an important factor that may influence therapeutic consistency, production scalability, and clinical applicability. While autologous sources increase costs and complicate the process, allogeneic sources allow for standardization and off-the-shelf product development. Exosome engineering makes it possible to direct and optimize immunomodulatory components to the target tissue, while combination therapies with biological agents can improve treatment efficacy. Long-term clinical trials could provide more data on the safety and efficacy of MSC exosomes and clarify their role in autoimmune diseases.

FOOTNOTES

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Country of origin: Türkiye

ORCID number: Fatma Sengul Bag 0000-0002-7097-6266; Omer Faruk Bag 0000-0002-6842-5342.

S-Editor: Wang JJ

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P-Editor: Zhang XD

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