Molecular Biology Reports
https://doi.org/10.1007/s11033-019-04588-y

REVIEW

Mesenchymal stem cell-based therapy for autoimmune diseases: emerging roles of extracellular vesicles

Fariba Rad[1] · Mohammad Ghorbani[2] · Amaneh Mohammadi Roushandeh[3] · Mehryar Habibi Roudkenar[4,5]

Received: 16 August 2018 / Accepted: 3 January 2019

Abstract

In autoimmune disease body's own immune system knows healthy cells as undesired and foreign cells. Over 80 types of autoimmune diseases have been recognized. Currently, at clinical practice, treatment strategies for autoimmune disorders are based on relieving symptoms and preventing difficulties. In other words, there is no effective and useful therapy up to now. It has been well-known that mesenchymal stem cells (MSCs) possess immunomodulatory effects. This strongly suggests that MSCs might be as a novel modality for treatment of autoimmune diseases. Supporting this notion a few preclinical and clinical studies indicate that MSCs ameliorate autoimmune disorders. Interestingly, it has been found that the beneficial effects of MSCs in autoimmune disorders are not relying only on direct cell-to-cell communication but on their capability to produce a broad range of paracrine factors including growth factors, cytokines and extracellular vehicles (EVs). EVs are multi-signal messengers that play a serious role in intercellular signaling through carrying cargo such as mRNA, miRNA, and proteins. Numerous studies have shown that MSC-derived EVs are able to mimic the effects of the cell of origin on immune cells. In this review, we discuss the current studies dealing with MSC-based therapies in autoimmune diseases and provide a vision and highlight in order to introduce MSC-derived EVs as an alternative and emerging modality for autoimmune disorders.

Keywords Autoimmune diseases · Mesenchymal stem cells · Extracellular vesicles · Cell-free therapy · Immune cells

Introduction

Autoimmune disorders occur when the body is not able to distinguish between self and non-self. In other words, in this condition, the immune system mistakes part of our body as foreign thereby attacks and destroys self-molecules [1, 2]. Correspondingly, autoimmune diseases are estimated to affect at least 2–5% of the population in developed countries, and the incidence is increasing. Many of these diseases are common in the 20- to 40-year age group. They are also more common in women than in men. Autoimmune diseases are usually chronic and often debilitating; with an enormous medical and economic burden [3]. Autoimmune diseases are antibody-mediated diseases. Conspiciously, the antibodies can either bind to antigens on particular cells or in extracellular tissues or by antigen–antibody complexes that form in the circulation and are deposited in vessel walls. In organ-specific disease the antibody is directed toward antigens in a single organ. Addison disease is an example of organ-specific disease, in which autoantibodies attack the myasthenia gravis and adrenal cortex in which they attack neuromuscular cells [3–5].

By contrast, systemic autoimmune diseases are a broad range of related diseases in which the immune cells attack autoantigens and resulted in inappropriate inflammation and affect multiple tissues and organs, although some sites are particularly susceptible, such as kidneys and joints [4, 5].

Based on the preclinical and clinical studies, it has been shown that the cytokines belonging to proinflammatory cytokines produced by M1 macrophages, Th1 and Th17

✉ Mehryar Habibi Roudkenar
roudkenar@gums.ac.ir

1 Cellular and Molecular Research Center, Yasuj University of Medical Sciences, Yasuj, Iran

2 Department of Hematology and Blood Banking, Gonabad University of Medical Sciences, Gonabad, Iran

3 Medical Biotechnology Research Center, Paramedicine Faculty, Guilan University of Medical Sciences, Rasht, Iran

4 Cardiovascular Disease Research Center, Department of Cardiology, School of Medicine, Heshmat Hospital, Guilan University of Medical Sciences, Rasht, Iran

5 Neuroscience Research Center, Guilan University of Medical Sciences, Rasht, Iran

Published online: 08 January 2019

cells (TNF, IFN-gamma, IL-12, IL-18, IL-22 IL-23, IL-17, MIF) contribute to the initiation of autoimmune diseases, whereas, anti-inflammatory cytokines (IL-4, IL-10, IL-13 IL-35, TGF-beta) that are produced from M2 macrophages decrease the inflammation and alleviate the condition. It has been revealed that Th1 cells and their proinflammatory cytokine such as IL-17 and IL-22 have been implicated in the pathogenesis of RA. Furthermore, based on studies conducted on RA animal model and RA patients, it has been shown that there was a significant association between weak response of anti-TNF therapy and the higher level of Th17 cells and their cytokine especially IL-17. Meaningly, these findings have led to focus of studies on the inhibition of Th17 cells pathway signaling and their producing cytokines especially co-inhibition of both IL17 and IL22 [6].

Initially, it has been shown that Th1 cells and their cytokine are implicated in Guillain–Barre syndrome (GBS), an immune-mediated acute inflammatory disorder in the peripheral nervous system (PNS), and also it is confirmed for its animal model i.e. autoimmune neuritis (EAN). However, recent studies have been indicated that the pathogenesis of GBS/EAN is much more complicated and other cells such as Th17, Th2, and Treg, could be attributed in the disease. In this account, the net effects of Th cytokines play important roles in the pathogenesis of EAN and GBS [7].

A number of studies have been revealed that MS patients had an elevated level of serum IL-23 and IL-17 and had a higher proportion of Th17 cells in peripheral blood. In other words Th17 cells and Th17-related cytokines may be implicated in the pathogenesis of MS [8].

Macrophage migration inhibitory factor (MIF) is another pro inflammatory type 1 cytokine that plays a crucial role in several inflammatory autoimmune diseases. For example, increased MIF plasma levels has been found in GBS patients as compared to healthy controls and interestingly there was a positive correlation between MIF circulating concentration and patient's disability. Moreover, monoclonal antibody or a chemical inhibitor of MIF effectively decreased the severity score reduced disease duration in murine EAN highlighting that targeting MIF could be a promising therapy for inflammatory demyelinating peripheral nerve disorders [9].

It also has been shown that MIF and its homolog D-dopachrome tautomerase (D-DT) contribute in the development of progressive male multiple sclerosis (MS) subjects. Interestingly, lacking of MIF and D-DT ameliorates the disease severity of the murine model of MS, autoimmune encephalomyelitis [10].

This findings were further supported in other mouse model of MS i.e. Experimental Allergic Encephalomyelitis (EAE) which indicate there is an important role of the MIF pathway in MS ethiopathogenesis and that interventions specifically blocking MIF receptors might be considered as therapeutic strategy in the clinical setting [11].

On the other hand, upregulated function of some anti-inflammatory cytokines such IL-4 and IL-13 and TGF-beta are implicated in some autoimmune diseases. Usually, IL-4 and IL-13 are considered as T helper 2-associated immune responses (i.e., type 2 immunity). Up regulated functions of IL-4 and IL-13 have been reported to implicate in the allergic response. Therefore, Therapeutic targeting of the IL-4/IL-13 pathway might be employed as a therapeutic strategy for treatment of patients suffering from allergic diseases such as asthma, atopic dermatitis, and eosinophilic esophagitis [12].

However, for treatment of other diseases such as neurodegenerative diseases, osteoporosis and diabetes might require the enhancement of IL-4 and/or IL-13 activities highlighting the pleotropic and complex functions of these two cytokine in disease pathophysiology.

Upregulated function of other anti-inflammatory cytokine, TGFß, has been reported as a key cytokine in the hepatic fibrosis. Targeting of TGFß either by direct inhibition or interferon (IFN) gamma therapy, given the antagonizing effect of IFN gamma on TGFß, have been resulted in improvement of in both liver inflammation and fibrosis [13].

It is really important to mention that the pro and anti-inflammatory cytokine hypothesis in autoimmunity is not a rule as certain autoimmune diseases such as SLE seem to depend on the combined action of pro and anti-inflammatory cytokines. It this way, the precise role of inflammatory of anti-inflammatory cytokines in SLE is still controversial and requires further and intense investigations to utilize cytokine-based therapies for treatment of SLE [14].

Considerably, the endogenous cytokine network in autoimmune diseases might play an important role in terms of effectiveness of therapy. The relevance of the endogenous cytokine network in autoimmune diseases is highlighted by the fact that certain drugs used in autoimmune diseases seem to act by modulating the endogenous cytokine network and naturally occurring inhibitors of pro inflammatory cytokines such as IFN-beta and corticosteroids that increases blood levels of TGF-beta and IL-1 receptor type II and IL-1 receptor antagonist in multiple sclerosis, anti-TNF-alpha mAb that increases TGF-beta in rheumatoid arthritis and tecfidera that increases blood levels of IL-4 in multiple sclerosis [15–18].

Therefore, the understanding of the contribution of pro inflammatory cytokines to the pathogenesis of certain autoimmune diseases has led to the advent of biologics for the treatment of autoimmune diseases. The first biologic was anti-TNF-alpha mAb approved 20 years ago for the treatment of RA. There are now several specific inhibitors of pro inflammatory cytokines in the clinical setting including antagonists of IL-1, TNF-alpha, IL-17A, IL-6, IL-12/23 that are used for the treatment of RA, IBD and psoriasis [19–21].

However, treatment of autoimmune diseases by biologics has been also resulted in several limitations including

high costs, immunogenicity with development of neutralizing antibody and the side effects (lymphoma and de novo induction of autoimmune diseases) [22, 23].

For example, monoclonal antibodies and fusion proteins to block TNF in patients with RA have been considered as a an important milestone for treatment of RA disease. However, due to induction of Antidrug antibody (ADAs) drug safety and efficacy might be affected. Furthermore, ADAs have an important role in causing a secondary response failure. In other words, efficacy of the biologic (TNF inhibitor) will be lost over time despite a good initial response [24, 25].

About 80 types of autoimmune disorders that may affect different systems and organs in the body have been reported. So far, there is not a real and effective therapy for autoimmune diseases and the conventional immune suppressive agents such as methothrexate, steroids and infliximab act to alleviate symptoms. Furthermore, these treatments have long-term side effects, as well as a need for life-long treatment [1, 2]. Therefore, an alternative and more efficient therapy strategy for treatment of autoimmune diseases has always been considered by both basic and clinical scientists. Interestingly, recently it has been found that mesenchymal stem cells (MSCs) might be as a novel therapeutic option for autoimmune disorders [26].

Relatively, multipotent MSCs have a variety of useful applications including unique immune properties [27–31]. Over the last decade, MSCs have been reported to possess a marked immune-regulatory effect against autoimmune disorders. For instance, MSCs are able not only to inhibit natural killer (NK) proliferation and activity but also suppress T/B cell proliferation and dendritic cells (DC) maturation [29, 32]. Because of these clinically relevant features, MSCs have gained much more interest for application in autoimmune disorders.

Recently, growing evidence has been indicated that the beneficial effects of MSCs in autoimmune disorders are not relying only on direct cell-to-cell interaction but on the paracrine action of MSCs [27, 32, 33]. Moreover, bodies of studies have shown that only a small proportion (typically less than 1%) of culture- expanded MSCs survive and incorporate into host tissues indicating the therapeutic effects of MSCs cannot be fully explained by direct cell-to-cell interaction [33–36].

Importantly, MSCs-based therapy for many diseases including autoimmune disorders, could be due to either producing of a vast array of biomolecules such as proteins, mRNA, and microRNAs through the release of secretory growth factors or extracellular vehicles (EVs) [27, 30–32, 34, 36, 37].

Though the physiological role of MSC- derived EVs is not currently well understood, several studies indicate that they play an important role in tissue repair and anti-cancer therapy [33–35].

Numerous studies have been shown that EVs, similar to MSCs, involve in some physiological functions such as cell proliferation and differentiation, genetic exchanges, antigen presentation, angiogenesis, tumor metastasis and immune system responses [34]. Furthermore, the ability of MSC-derived EVs to mimic the effects of the cell of origin has been studied on various different effector cells. MSC-derived EVs not only contribute to the recovery of damaged tissue and the manipulation of the immune system but also they do not represent the disadvantages of their original cells [34]. It is noteworthy to mention that stem cells therapy raised several concerns including immune rejection, senescence, low cell survival and concern about the possibility of cancer formation [30, 33, 34, 38–40]. Furthermore, genetic manipulations of MSCs can increase the oncogenic potential of the cells. In the light of these observations, the clinical applications of MSCs should be concerning [33, 41].

In this review, we discussed and focused on the recent findings dealing with the application of MSC for therapeutic purposes in autoimmune diseases by highlighting the importance of MSC-derived EVs and also the mechanisms by which MSCs or MSC-derived EVs suppress an immune response.

Immunosuppressive potential of MSCs

MSCs are a rare, heterogeneous population of non-hematopoietic stem cells that originally reported by Friedenstein in 1976 as a fibroblast- like cellular population in bone marrow (BM) [42, 43]. Johnson and Dorshkind in 1986 and Pittenger et al. in 1999 isolated MSCs from BM by density gradient centrifugation to eliminate unwanted cell types. They showed only 0.001 to 0.01% of the cells isolated from the density interface were MSCs that provide the structural and functional support for hematopoietic stem cells (HSCs) in their niche [34]. Although MSCs were traditionally and generally isolated from bone marrow, but it was subsequently shown that MSCs can be obtained from a variety of sources such as adipose tissue, skeletal muscle, synovium, the circulatory system, peripheral blood, dental pulp, liver, lung, amniotic fluid, placenta and umbilical cord (UC) [30, 34, 44, 45]. In 2006, the International Society of Cellular Therapy (ISCT) defined MSCs by three criteria including adhesion properties to plastic under standard tissue culture conditions, expression of certain cell surface markers such as CD73, CD90, and CD105, and no expression of other markers including CD45, CD34, CD14, or CD11b, CD79 alpha or CD19 and HLA-DR surface molecules and the differentiation capacity into osteoblasts, adipocytes, and chondroblasts under in vitro conditions [46, 47]. MSCs of all sources are able to exert a range of biological functions (Fig. 1). The immunosuppressive effects are the well-known functions of MSCs. In other words, this indicates that MSCs could have

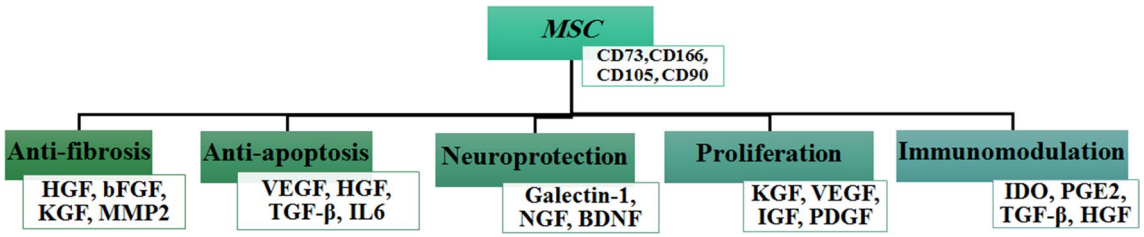

Fig. 1 Biological functions of mesenchymal stem cells. MSCs are able to exert a wide range of biological functions. *HGF* hepatocyte growth factor, *bFGF* basic fibroblast growth factor, *KGF* keratinocyte growth factor, *MMP*-2 metalloproteinase-2, *VEGF* vascular endothelial growth factor, *TGF-β1* transforming growth factor, *IL-6* interleukin-6, *NGF* Nerve growth factor, *BDNF* brain derived neuron trophic factor, *IGF* Insulin-like growth factor, *VEGF* vascular endothelial growth factor, *PDGF* platelet-derived growth factor, *IDO* indoleamine 2,3-dioxygenase, *PGE2* prostaglandin E2

therapeutic potential for treatment of autoimmune diseases. In fact, the immunosuppressive properties of MSCs have been shown in several in vitro and in vivo studies [48–50].

In human, MSCs express moderate expression level of human leukocyte antigen (HLA) major histocompatibility complex class I with no expression of major histocompatibility complex class II and no expression of co-stimulatory molecules (CD80, CD86 and CD40, CD40L) [51–56]. In addition, researchers have found that MSCs use mechanisms that involve cell contact and secretion of different molecules during the regulation of the immune responses (Fig. 2).

MSCs-derived cytokines/growth factors play an important role in the immune suppressive potential of MSCs. IFNγ is one of these molecules and play an important role in immune modulatory property of MSCs. IFNγ usually exerts the immune modulatory effects together with other cytokines such as TNF- α, IL-1 α, IL-1ß or IL-17. Moreover, IFNγ induces the expression of regulatory molecules such as vascular cell adhesion molecule 1 (VCAM-I), intercellular adhesion molecule 1 (ICMA-1), Jagged-1 and 2, programmed death-ligand 1 (PD-L 1) and human leukocyte antigen G1 (HLAG1) in the immune response [27, 57–59]. Moreover, other immunomodulatory molecules such as interleukin-10 (IL-10), hepatocyte growth factor (HGF), transforming growth factor β (TGF-β), indoleamine 2,3-dioxygenase (IDO), interleukin-6 (IL-6), galectin

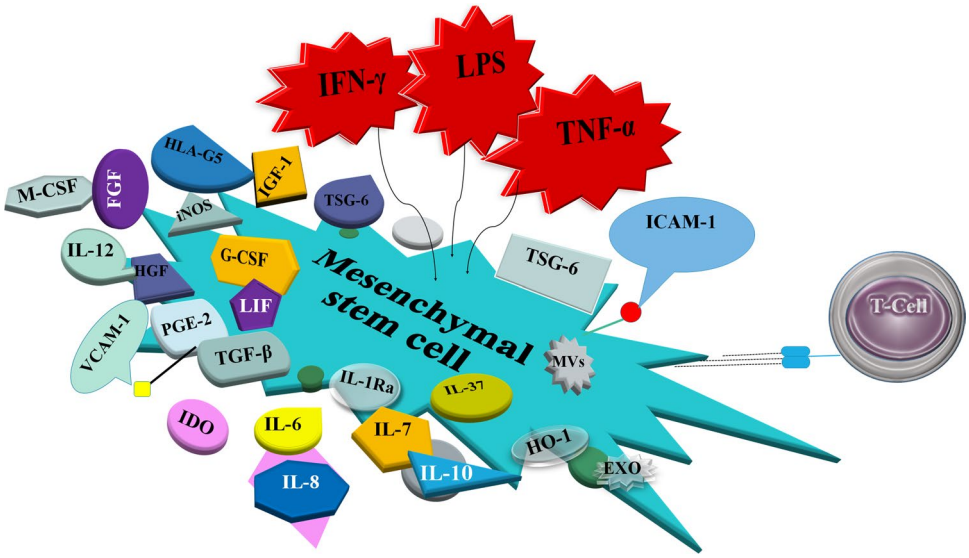

Fig. 2 MSC-derived immunomodulatory cytokine/growth factors. Upon an inflammatory microenvironment, MSCs activate and express immunosuppressive molecules. MSCs obtain immunomodulation function through mechanisms that involve cell contact and secretion of different molecules such as IL-10, IL-6, PGE-2 and TGF-β. IL-6; interleukin-6, IL-8; interleukin-8, IL-7; interleukin-7, IL-37; interleukin-37, *IL-1Ra* interleukin-1Ra, *TGF-β1* transforming growth factor, *IDO* indoleamine 2,3-dioxygenase, *VCAM*-1 vascular cell adhesion molecule 1, *PGE2* prostaglandin E2, *HGF* hepatocyte growth factor, *IL-12* interleukin-12, *M-CSF* macrophage colony-stimulating factor, *FGF* fibroblast growth factor, *HLA*-G5 human leukocyte antigen-G molecules, *G-CSF* granulocyte-colony stimulating factor, *IGF* Insulin-like growth factor, *TSG*-6 TNF-stimulated gene 6 protein, *IF*γ interferon gamma, *LPS* lipopolysaccharides, *TNF*-α tumor necrosis factor-α *ICAM*-1 intercellular adhesion molecule 1, *MVs* microvesicles, *Exo* exosome

(Gal)-1, and nitric oxide (NO) that modulate innate and adaptive immune responses are secreted by MSCs [27, 58, 59]. MSCs suppress T-cell proliferation, cytokine secretion, regulate the balance of Th1/Th2, modulate the regulatory T cells (Tregs), and regulate B-cell activity and antigen presentation of dendritic cells [60–63]. As mentioned, one of the immunomodulatory functions of MSCs is to promote regulatory T cells (Tregs). It has been revealed that some MSC-derived soluble factors such as TGF-β1, HLA-G4, and PGE2 act as Treg inducers [64].

Notably, MSCs can reduce pro-inflammatory cytokines, comprising tumor necrosis factor (TNF), and repressing inflammation. As mentioned above, TNF is a master mediator of the pathogenesis of autoimmune diseases and chronic inflammation. It has been shown that TNF can deregulate the balance between Tregs and pathogenic Th1 cells and Th17 in RA patients and impairs Treg functions in MS and RA patients [55, 56].

Consequently, MSCs at least in part by anti-TNF property could be employed as a therapeutic modality for autoimmune diseases.

It is well worth to mention that TNF, IFNγ, and IL-1 in inflammatory tissues might strengthen the immunosuppressive functions of MSCs [36–38]. Supporting this notion, it has been shown that, pre-treatment of MSCs with IFNγ increased the immunosuppressive potential [39]. Additionally, it has been revealed that other immunosuppressive molecules, chemokines and growth factors such as TGFβ, IL-8, and TSG-6, were produced by TNF-primed MSCs are able to attenuate the symptoms in diseases including myocardial infarction, EAE, cutaneous wound,, and ischemic hind limb likely via TNFR1 signaling path way [65, 66].

Immunosuppressive functions of MSCs could also be owing to production of TGF-β by this cells. MSC-derived TGF-β1 regulates the activity of NK cells, T cells, mast cells, macrophages/microglia [67, 68]. MSC-derived TGF-β1 also plays an important modulation role in differentiation of T helper (Th) subsets. For example, it has been shown that overexpression of TGF-β1 in mBM-MSCs improved their therapeutic potential in a model of type 1 diabetes with an increased Th2 response [69, 70].

MSCs are able to inhibit B-cells proliferation and antibody production in the presence of IL40, CD40L, cytosine–phosphate–guanosine (CpG), interleukin (IL)-2, anti-immunoglobulin, and IL-4. Interestingly, they had no effect on B-cells following stimulation by CpG and allogeneic T-cell-depleted peripheral blood mononuclear cells (PBMCs). However, the immunomodulatory effects of MSCs on B-cells are still unclear and even controversial. Moreover, MSCs affect the maturation of dendritic cells (DC) by down-regulating of MHC class II and co-stimulatory molecules expression [71–74]. MSCs also modulate expression of IL-10 and IL-12 [75]. MSCs trough expression of high level of TGF- γ decreases the proliferation of NK cells and increases differentiation of Treg lymphocytes CD4 + CD25 + Foxp3+ [76]. It has been revealed that MSCs can delay the apoptosis of neutrophils preserving and prevent infections [77]. It is noteworthy that the interaction between immune cells and MSC is bidirectional [78]. The immunomodulatory effects of MSCs on immune cells have been shown in Fig. 3.

Of note, regarding the action of mesenchymal stem cells in autoimmune diseases there is a possible interference of this treatment via production of cytokines on the signaling pathway that dysregulation of which may be implicated in the pathogenesis of certain autoimmune diseases. For example, it has been demonstrated that MSCs via the production of IL-6 suppress cell proliferation of astrocytes and activate its downstream AMPK/mTOR signaling pathway, thereby exerted their therapeutic effects by improvement of memory and learning impairment of hypoxic-ischemic brain damage (HIBD) rats.

Interestingly, down regulation of IL-6 expression in MSCs abolished the above regulatory functions of MSCs in hippocampal astrocytes. Furthermore, by utilization of rapamycin (inhibitor of AMPK/mTOR signaling pathway) it was confirmed that mTOR involved in the proliferation of reactive astrocytes [79].

Noticeably, it is required to say that the PI3K/AKT/mTOR pathway, as an intracellular signaling network, regulates proliferation, cell activation, apoptosis, and metabolism. A number of studies suggest that the deregulation of PI3K/AKT/mTOR pathway might be implicated in autoimmunity. For example, it has been revealed that there is an involvement of PI3K/AKT/mTOR pathway in the etiopathogenesis of MS. Supporting this notion, it has been shown that targeting of PI3K/mTOR pathway by rapamycin, an immunosuppressive drug that has been widely used to treat some autoimmune disease, has been resulted in the improvement of MS symptoms [80].

Importantly and interestingly, rapamycin does not block proliferation of regulatory T cells (Tregs) [81]. Therefore, down modulating the mTOR pathways may represent an additional important tool by which mesenchymal therapy dampens autoimmune diseases.

MSC-based therapy in autoimmune diseases

Autoimmune diseases are more prevalent in women and considered as the second leading cause of chronic illness in the United States [82]. The conventional therapies not only are not so efficient but also having long-term side effects. Therefore, alternative and new modality for treatment of autoimmune diseases is needed. MSC-based therapy would be one of the versatile and promising strategies for treatment of autoimmune diseases. Supporting this notion, the

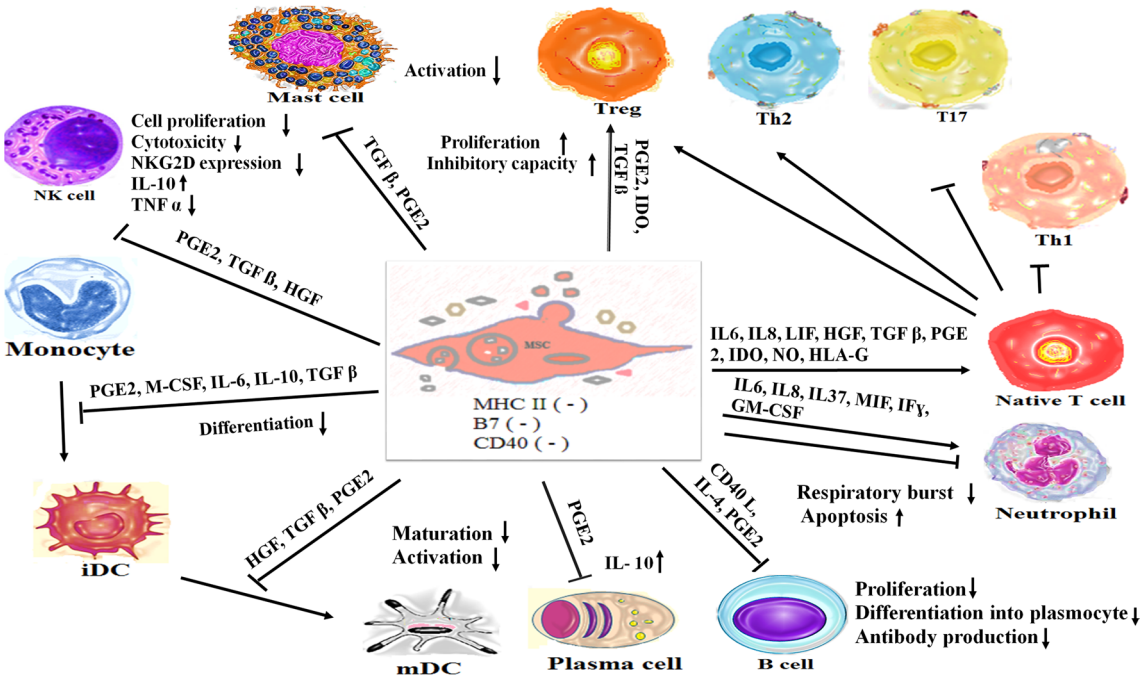

Fig. 3 Immunomodulatory property of MSCs. MSCs can target lymphocytes, regulatory T-lymphocytes (Tregs), B-lymphocytes, Plasma cells, Natural killer (NK) cells, neutrophils, mast cells, monocytes, and dendritic cells. These effects may be mediated by cell contacts, soluble factors and MSC-derived EVs. *LIF* leukemia inhibitory factor, *HGF* hepatocyte growth factor, *TGF*-β1 transforming growth factor, *PGE2* prostaglandin E2, *IL*-4 interleukin-4, *IL*-6 interleukin-6, *IL*-8 interleukin-6, *IL-37* interleukin-37, *IFγ* interferon γ, *IL-10* interleukin-10, *GM-CSF* Granulocyte–macrophage colony-stimulating factor, *IDO* indoleamine 2,3-dioxygenase, *NO* nitric oxide, *M-CSF* macrophage colony-stimulating factor, *IL-10* interleukin-10, *HLA-G* human leukocyte antigen G

application of MSCs for treatment of autoimmune diseases has been shown in a number of animal models and clinical trials (Tables 1, 2).

Cell-free therapy for autoimmune diseases

Recently, many scientists believed that the beneficial effects of MSCs are owing to the paracrine activity of MSCs not to their cell replacement properties and/or differentiation properties [34, 92–94]. The paracrine activity of MSCs could be considered as a novel therapeutic perspective in order to develop a safe and potentially more advantageous alternative to MSC-based therapy i.e. cell-free strategies. Notably, MSC-derived EVs are an example of the paracrine activity of MSCs. In below MSC-derived EVs will be discussed in more detail.

MSC-derived extracellular vesicles

Early studies have described EVs as 'garbage bags' by which cells eliminate unwanted proteins and other molecules [95]. EVs, or more accurately nanoparticles, Size 30–1000 nm, are a term used for vesicles that are enclosed by a phospholipid bilayer and released either during cell stress or under basal conditions [96–99]. Furthermore, they also play a crucial role in the development and progression of diseases [100]. MSCs also can release several types of EVs [97]. The International Society for Extracellular Vesicles has suggested that the term EVs can be used preferentially to describe prepared vesicles from body fluids and cell cultures. Recently, EVs are classified into two major groups Exosomes (Exos) and Microvesicles (MVs) based on their biogenesis, molecular mechanisms underlying the release of EVs and size [93, 97, 101].

Exosomes are cup-shaped or rounded EVs with a diameter of 30–130 nm. They can be isolated by ultracentrifugation at 100,000×*g* or above for 1–2 h [96, 102, 103]. Alix, Tsg101, tetraspanins, CD9, CD63, and CD81 are associated markers with exosomes [33, 98, 104, 105]. Of note, ExoCarta database contains a comprehensive list of proteins, lipids, and RNAs associated with MVs (http://www.exocarta.org) [104].

Exosomes are the only class of EVs known to be derived from early endosomes through the invagination of the endosomal membrane to form a multi vesicular body (MVB) or late endosomes with numerous ILV [33, 96, 97]. The budding of ILVs from the late endosomes and amalgamation of these MVBs with the plasma membrane require some factors such as Rab and Ral GTPases, SNAREs, and the V-type ATPase [106].

Table 1 Preclinical studies of MSCs application in autoimmune diseases

Source	Administration way of MSCs	Outcomes/mechanisms	Model	Ref.
Murine BMSCs	IV	• MSCs inhibited T-cell proliferation • MSCs did not induce apoptosis on T cells	EAE	[83]
Murine BMSCs	IV	• MSCs did not have any effect on CIA model • The suppressive effect of MSCs on the proliferation of T cell altered by adding TNFα	CIA	[84]
hAD MSCs	IP	• MSCs decreased production of various inflammatory cytokines and chemokines • hAD-MSCs reduced Th1/Th17 cell expansion • MSCs induced de novo generation of antigen specific CD4 + CD25 + FoxP3 + Treg cells	CIA	[85]
Murine BMSc	IV	• MSCs reduced the severity of arthritis • MSCs reduced antibody titer and level of • MSCs increased level of IL-4 in spleen cells	CIA	[86]
Canine AD-MSCs	ID	• Immonomodulatory factors of MSCs such as TGF-β, PGE2, HGF, and IDO improved keratoconjunctivitis sicca	Dog with keratoconjunctivitis sicca	[87]
Murine ADMSC	IP	• Down-regulation of the CD4 + Th1 and expansion of Tregs in the pancreatic lymph nodes led to improvement of NOD	NOD	[88]
Murine BMSCs	IP	• MSC conditioned medium inhibited EAE-derived CD4 T cell activation by suppressing STAT3 phosphorylation via MSC-derived CCL2 • MSCs modulated EAE biology via the paracrine conversion of CCL2 from agonist to antagonist of CD4 Th17 cell function	EAE	[89]
hBM MSCs	Retro-orbital injection of the venous sinus	• MSCs attenuated lupus nephritis by suppressing the development of Tfh cells and the subsequent activation of humoral immune components	NZBxNZW F1 mice	[90]
Mouce BMSCs	IP	• MSC therapy was not beneficial in Th2-type T cell- and B cell-driven diseases such as lupus	NZBxNZW F1 mice	[91]

hMSCs human bone marrow-derived mesenchymal stem cells, *IP* intraperitoneal injection, *NZBxNZW F1 mice* a model of systemic lupus erythematosus, *m-BMSCs* mice bone marrow-derived mesenchymal stem cells, *Treg* regulatory T cells, *EAE* experimental autoimmune encephalomyelitis, *TGF-β* transforming growth factor beta, *PGE2* prostaglandin E2, *HGF* hepatocyte growth factor, *CCL2* C–C motif chemokine ligand 2, *NOD* non obese diabetic, *IL-4* interleukin 4, *IL-6* interleukin 6, *IL-10* interleukin 10, *AD-MSCs* adipose tissue-derived mesenchymal stem cell, *CIA* collagen-induced arthritis, *IV* intravenous injection, *Th1* T helper 1, *Th17* T helper 17, *Tfh* Follicular helper T, *ID* intra dermal

Micro vesicles (100–1000 nm) are arising from the budding of the plasma membrane through the reorganization of membrane phospholipids and increased concentration of Ca^{2+} that activates enzymatic cascade [34, 98]. ADP-ribosylation factor 6 (ARF6), ADP-ribosylation factor 1 (ARF1), Rab, Rac1 (also known as Ras-related C3 botulinum toxin substrate 1) and Ras homolog family member A (RhoA) are required for cargo sorting and micro vesicle shedding [107]. As previously described, a wide range of molecules, including cytokines, growth factors, as well as miRNA have been identified in MSC-derived MVs (more than 700 proteins and 150 miRNAs).

Implication of MVs in regeneration of a number of tissues such as liver, kidney, heart, and nervous tissues has been reported [108–114]. MVs can be isolated by centrifugation, 16,000–20,000×*g* for 70–90 min at 4 °C [97].

It is worth mentioning that the more recent findings have been revealed the complexity and overlapping characteristics of these nanoparticles [115]. However, in this review we use "extracellular vesicles" (EVs) for all secreted vesicles.

Mechanism of action

Originally, it was believed that EVs are cellular debris without important biological function. However, a number of studies indicate that EVs have a crucial role in both physiological and pathological conditions, modulation of the immune response, intracellular signaling, inflammation, and maintenance of homeostasis, cancer progression, angiogenesis, and coagulation [116, 117]. Supporting this notion, it has been shown that EVs might be considered as diagnostic, prognostic, and treatment monitoring biomarker [118].

EVs lipid bilayer membrane has transmembrane proteins and encloses nucleic acids and soluble proteins derived from the cell of origin [119]. EVs are able to shuttle lipids, carbohydrates, protein, lipids, messenger RNAs, long non coding RNAs, micro RNAs, and mitochondrial DNA into target cells [120, 121].

miRNA-carrying EVs have been shown to implicate in the immune synapsis between antigen presenting cells and T-cells. Furthermore, EV-mediated transfer of miRNAs

Table 2 Clinical trials of MSCs application in autoimmune diseases (Clinical Triales.gov)

Identifier	Condition/disease	Intervention/treatment	Aim of study	Enrolment	Phase	Status
NCT01741857	SLE	Biological: hUC-MSCT for SLE	Safety and efficacy of allogeneic MSCT to treat patients with active and refractory SLE who have been resistant to multiple standard treatments	40	I/II	Unknown
NCT03219801	SLE	Biological MSC	Evaluate the safety and efficacy of hUC-MSCT in SLE	10	Early phase 1	Not yet recruiting
NCT01895439	MS	Biological: autologous MSC	Safety and efficacy study of autologous BMSC in multiple sclerosis	13	I/II	Completed
NCT01322789	DM, insulin-dependent	Biological: intravenous MSC infusion	Safety and efficacy of MSC in newly-diagnosed type 1 diabetic patients	10	I/II	Unknown
NCT01540292	Crohn's disease	Biological: MSC	Assess safety and efficacy of allogeneic MSC in Crohn's disease refractory or intolerant to conventional therapies	20	I/II	Unknown
NCT03326505	MS	Biological: UCMSC Other: supervised physical therapy	Expanding MSCs to a clinical scale according to good laboratory practice and study its efficacy when compared to a supervised physical therapy program alone	60	I/II	Recruiting
NCT01374854	T1DM	Biological: UC-MSCs infusion Drug: traditional therapy	USC-MSCs can affect beta-cell in T1D patients through multiple signals and improve diabetic control	44	I/II	Unknown
NCT01854957	M SI	Biological: autologous MSC	Evaluate the safety and the efficacy of the intravenous administration of autologous MSC to patients with MS resistant to currently available therapies	20	I/II	Unknown
NCT00395200	MS	Procedure: MSC treatment	Establish the safety of intravenous administration of BMSC autologous adult to patients with MS	10	I/II	Completed
NCT02633163	SLE	Drug: low dose MSCs Drug: high dose MSCs Drug: placebo infusion	The purpose of this study is to evaluate the efficacy and safety of UC-MSCs obtained for the treatment of SLE in adult patients	81	II	Not yet recruiting
NCT01661842	AIH	Other: conventional plus UC-MSC treatment Other: Conventional plus placebo treatment	The safety and efficacy of UC-MSC transplantation for AIH patients will be evaluated	100	I/II	Unknown
NCT02643823	RA	Biological: hUC-MSC + DMARDs Drug: DMARDs	The purpose of this study is to evaluate the safety and efficacy of hUC-MSC for RA	40	I	Unknown
NCT01143168	T1DM	Biological: autologous BMSC and UCMSC	The purpose of this study is to evaluate the feasibility, efficacy and safety of transplantation therapy using BMSC and UCMSC for patients with type 1 diabetes mellitus	24	I	Unknown

Table 2 (continued)

Identifier	Condition/disease	Intervention/treatment	Aim of study	Enrolment	Phase	Status
NCT01539902	Lupus nephritis	Biological: hUC MSCs Drug: cyclophosphamide	The efficacy measure of hUC-MSC in the treatment of proliferative lupus nephritis on remission of lupus nephritis (combined partial and complete remission) in terms of stabilization and improvement in renal function	25	II	Recruiting
NCT01873625	RA	Biological: MSCT Biological: Placebo	The aim of evaluating therapeutic effects of intra-articular injection of BM-MSCs in patients with knee osteoarthritis	60	II/III	Completed
NCT01068951	T1D	Biological: MSC	The main hypothesis of the study is that the development of autoimmune diabetes may be halted at diagnosis by the immune modulatory properties of mesenchymal stem cells	20	Not applicable	Completed

MS multiple sclerosis, *SLE* systemic lupus erythematosus, *HUC-MSCT* human umbilical cord-derived mesenchymal stem cells transplantation, *MSC* mesenchymal stem cells, *T1DM* type 1 diabetes, *AIH* autoimmune hepatitis, *RA* rheumatoid arthritis

might allow communication between dendritic cells, affect their function [122].

Bruno et al. studied the effect of MSC-derived EVs with that of the cell of origin in an experimental model of AKI [111]. Interestingly, they have been found that the EVs were able to mimic the effect of MSCs resulting in the morphological and functional recovery of AKI. These studies indicate that EVs derived from stem cells by induction of epigenetic changes and modulations of gene transcription in recipient cells stimulate tissue regeneration [122]. In other words, EVs by delivering bioactive lipids, proteins, and nucleic acids can transfer the imprinting of the originator cells to the recipient cells. Moreover, Quesenberry group revealed that the cell cycle status and the injury of the originator cells implicate in the epigenetic changes observed in bone marrow cells [122, 123].

The protein content of EVs derived from human bone marrow-derived MSCs and human CD133+ cells were profiled by Angulski et al. [67]. They have been found that although the EVs from both origins were qualitatively similar, hMSC-EVs might induce/modulate more efficiently differentiation, migration, the metabolic state of the target cells, and phagocytosis and innate immune responses. On the other hand, the CD133+-EVs might be better modulators or inducers of angiogenesis than hMSC-EVs.

It has been found that the lipids belonging to the double layer membrane surrounding the EVs not only have structural functions, but also act as conveyors of membrane-derived bioactive lipids. EVs also have an important role in the "transcellular" synthesis of leukotrienes and prostaglandins. In other words, they represent an additional manner through which enzymes and substrates can be exchanged between cells [68].

Stem cell-derived EVs have been implicated in self-renewal, differentiation, maturation and cell fate determination of stem cells [124]. In this regard, the roles of EV-derived ncRNA are prominent and beginning to be explored. Several studies have been indicated that EV-ncRNAs play important roles in the paracrine effects of stem cells and even the most EV-mediated regulatory effects elicited in cells are mediated through ncRNAs [124, 125].

For example, EVs carrying let-7b, from preconditioned MSCs, have been shown to implicate in transition from inflammatory phase toward the proliferative phase and regulation of macrophage plasticity that involve in the resolution of chronic inflammation [126]. miR146a, miR-21, and miR-181 in the umbilical cord MSC-derived EVs have been shown to ameliorate inflammation during the tissue repair [127].

In vivo bio distribution of EVs

In order to use MSC-derived EVs for clinical applications, the first requirement would be an establishment of a suitable MSC culture condition based on GMP compliance to isolate and produce EVs. Therefore, for successful and safe clinical utilization of MSC-derived EVs investigation of EVs bio distribution upon administration is essential [128]. Wiklander et al. studied the bio distribution of EVs in mice after systemic delivery [129]. EVs were isolated from different cell sources and labeled with a near-infrared lipophilic dye. It has been revealed that while EVs accumulated mainly in spleen, liver, lung, and gastrointestinal tract differences related to EVs cell origin were observed. Furthermore, the dose of injected EVs and the route of administration affected the bio distribution pattern. These findings highlight that for future EVs-based therapy in the clinic, these should be considered.

Grange et al. investigated the bio distribution and the renal localization of EVs in AKI [130]. MSC-derived EVs were directly or indirectly labeled with near infrared (NIR) dye and were injected intravenously (i.v.) into glycerol-induced AKI mice model as well as into healthy mice. They have been found that the both labeling methods were suitable for the in vivo detection of the renal localization of EVs. Interestingly, it was revealed that MSC-derived EVs localized in injured, not normal kidneys, indicating their beneficial effects on recovery following AKI. However, So far there is no study dealing with the bio distribution pattern of EVs-based therapy for autoimmune diseases and warrants further studies in these regard.

In vitro effects of MSC-derived EVs on innate and adaptive immunity

A number of studies indicate that the immunomodulatory activity of MSCs could be attributed to MVs (Table 3) [34]. It has been revealed that MSC-derived MVs are able to have an inhibitory effect on both B and T cells [131, 132]. However, the precise effects of MSCs-derived EVs and their mechanisms remain unclear.

It has been found that murine BM-MSCs- derived MVs can induce apoptosis in activated T-cells as well as increase the proportion of regulatory T CD4 + CD25 + FoxP3 + cells [145].

Juan et al. reported that adipose MSC-derived EVs can increase the expression of CX3CR1 in F4/80+/Ly6C+/CCR2 + macrophage subsets in an acute experimental model (mouse) of thioglycollate-induced peritonitis and modulate an internal pro-inflammatory program in activated macrophages [33, 146]. Furthermore, it has been shown that the MVs could alter miRNAs profiles. Of note, miR-155 and miR-21 which are involved in inflammation are regulated by MSC-derived MVs [132, 147].

Surprisingly, it has been reported that MSC-MVs suppress activation of mast cells through reduction of pro-inflammatory cytokines release (especially TNF α), attenuation of protease activity (including tryptase and chymase), increasing of prostaglandin E2 (PGE2) production, and up-regulation of E-prostanoid 4 (EP4) receptor expression [148].

It has also been shown that hAMSC-derived EVs are able to down-regulate macrophage activation by suppressing Toll-like receptor signaling. Also, the EVs increased the proportion of Tregs and decreased the proportion of Th17 [69, 149].

The immunomodulatory effect of BMSCs and their EVs on monocyte-derived DCs has been investigated in type 1 diabetes. It was revealed that MSCs and MSC-derived EVs were able to inhibit the maturation and activation of DC [136].

In vivo studies dealing with MSCs-derived EVs as a novel emerging modality for treatment of autoimmune diseases

MVs have a potential to inhibit the rupture of an intracranial aneurysm in a mouse model through reduction of mast cell activity [148]. Favaro research team provided evidence indicates that MSC-MVs can prevent Th1 response via a variety of mechanisms including increasing the level of IL-10 cytokines, PGE2 and TGF-β [150].

The immunosuppressive effects of MSC-derived EVs have been reported in an immune- induced liver injury model. It has been found that MSC-derived EVs as well as MSCs can suppress Concanavalin A (Con A) -induced liver injury [151].

Therapeutic potential of MSC-derived EVs has been shown in a preclinical study of EAE. The EVs inhibited auto reactive lymphocyte proliferation and increased levels of transforming growth factor (TGF)-β and interleukin (IL)-10 and in splenic mononuclear cells [93].

Co-culture of THP-1 cells (a human monocytic cell line) with EVs has been resulted in shifting of activated CD4 + T cells to CD4 + CD25 + FoxP3 + regulatory T cells (Tregs) and improvement in the survival of allogeneic skin graft in mice [152].

Recently, the role of MSC-derived EVs in the reduction of arthritis signs in Collagen-Induced Arthritis (CIA) models has been shown. It was found that the EVs could exert their therapeutic effects through reducing of plasma blast cells and increasing B cells secreting IL-10 [134, 153].

In a model of multiple sclerosis, MSC-derived EVs inhibited auto-reactive lymphocyte proliferation and also increased the levels of IL-10 and TGF-β. Similarly, it has

Table 3 Preclinical studies of MSCs derived extracellular vesicles application in autoimmune diseases

Model	Source	Isolation procedure	EV dose	Administration way of EVs	Outcomes	Ref.
EAU model/rat	hUC—MSCs	Ultracentrifugation, 110,000 × *g* for 7 h	10, 20, 50, 100 µg	IP	EVs improve EAU by inhibiting the migration of inflammatory cells	[133]
CIA models/mouse	Mouse—BMSC	Ultracentrifugation, 100,000×*g* for 2 h for EXO and 8000×*g* for 1 h for EVs	250 ng, 600 ng	IV	EVs were more efficient in suppressing inflammation in CIA models	[134]
Human	hBMSC	Ultracentrifugation, 100,000×*g* for 2 h	1 unit[a] 4 unit	Transfusion	EVs can be utilized as an effective therapeutic tool to treat refractory GVHD and various diseases	[135]
Invitro	hBMSC	Ultracentrifugation, 100,000×*g* for ? h (no mentioned)	2.5 × 108/ml	Co-cultured	MSC and EV inhibited the maturation of DC cells and induce their regulatory in type1diabetic patients	[136]
Chimeric model of SLE	Unknown	Unknown	Unknown	Unknown	The result have not published yet (the study is running)	[137]
NOD model of SS/mouse	Human—iPSC-MSC	Ultracentrifugation, 100,000×*g* for 90 min	30 µg	IV	iPSC MSCs and their EVs inhibited the progression of SS before the onset of sialadenitis	[138]
T1D model/mouse	hMSC	Chromatography	3 µg and 30 µg[b]	IV	EVs inhibited autoimmunity in mouse models of T1D and prevent the onset of disease	[133]
EAU model/mouse	hMSC	Chromatography	30 µg[b]	IV	EVs delayed the beginning of disease in mouse model of EAU	[65, 133]
EAE model/mouse	hPDLSCs	ExoQuick-TC	≈ 1600 µg of hPDLSCs CM/moue /≈24 µg of hPDLSCs EMVs/ mouse	IV	hPDLSderived CM and purified EMVs attenuate the EAE development	[139]
T1DM model/mouse	AD—MSCs	Ultracentrifugation, 100,000×*g* for 70 min	50 µg	IP	EVs-derived AD-MSCs exerted the beneficial effects on autoimmune T1DM mouse model with increasing Treg population and anti-inflammatory cytokines such as IL-4, IL-10 and TGF- beta and through decreasing pro-inflammatory cytokines such as IFN gamma and IL-17	[140]
EAE model/mouse	hPDL-SCs	ExoQuick-TC	≈ 1600 µg of hPDLSCs-CM/moue/≈24 µg of hPDLSCs-EMVs/ mouse	IV	CM and EMVs derived hPDLSCs decreased the expression level of pro- inflammation cytokines such as IFN- γ, TNF- α, IL-17, IL-6 and IL-1 β and increase anti-inflammatory cytokines	[141]
TMEV model/mouse	hAD—MSCs	Ultracentrifugation, 100,000×*g* for 70 min	25 µg	IV	Administration of EVs- derived hAD-MSCs reduced motor defects through the regulation of the immune system, reduced brain atrophy and increased remyelination	[142]
CIA model/mouse	BM-MSCs engineered by miR-150-5p and miR-67	ExoQuick-TC	10 µgl	ID	Exo-150 exerted the therapeutic effect on joint destruction in CIA model through down regulation of VEGF and MMP14, reduced migration and inhibited angiogenesis process	[143]

Table 3 (continued)

Model	Source	Isolation procedure	EV dose	Administration way of EVs	Outcomes	Ref.
STZ-diabetic rats	ADSCs were isolated from paratesticular fat of rat	ExoQuick-TC	10 or 100 µg	IC	EVs-derived ADSCs carried miR-130a, miR-132, miR-126, miR-let7b and miR-let7c They induced proliferation of endothelial cells in vitro, decreased fibrosis and restored erectile function in vivo by these microRNA	[144]

NOD non obese diabetic, *iPSC-MSC* induced pluripotent stem cell-derived mesenchymal stem cells, *EVs* extracellular vesicles, *IV* intravenous injection, *CIA* collagen-induced arthritis, *SLE* systemic lupus erythematosus, *EAU* experimental autoimmune uveitis, *Huc* human umbilical cord, *IP* periocular injection, *GVHD* graft versus host disease, *DC* dendritic cell, *T1D* diabetes mellitus type 1, *hPDLSC* human periodontal ligament stem cell, *CM* condition medium, *AD-MSC* adipose tissue-mesenchymal stem cell, *TMEV* Theiler's murine encephalomyelitis virus (TMEV)-induced demyelinating disease, *BM-MSC* bone marrow-derived MSC, *ID* intradermally, *VEGF* vascular endothelial growth factor, *MMP*-14 matrix metalloproteinase-14, *IC* intracavernous

[a]The extracellular vesicles obtained from the supernatant of 4×10^7 MSCs were considered as an appropriate dosage (dose/kg) for this patient and was determined as 1 unit

[b]30 µg containing 15×10^8 and 15×10^9 EVs per mouse

been revealed that MSC-derived EVs after cell transplantation was a key factor to rescue bone marrow MSC function in lupus murine model [154].

The efficacy of MSC-derived EVs has been shown in a patient with refractory GVHD. Following the EVs therapy in the patients, improvement in the clinical GVHD symptoms were observed [135].

Autoimmune uveitis is one of the main reasons of visual disability around the world. The cause of uveitis is often unknown. It has been reported that periocular injection of human MSCs-derived EVs resulted in decreasing of experimental uveoretinitis (EAU) signs in rats [155].

So far as we know to date, despite the noteworthy results of MSCs-derived EVs to inhibit inflammatory responses in vitro and in autoimmune disease in preclinical, the effect of purified EVs has not been reported in the human and preclinical model of SLE. However, more recently, Sharma et al. stated that the effects of MSC-derived EVs is going to be examined in vivo using a chimeric model of SLE developed recently in their laboratory [137].

More recently, the ability of induced pluripotent stem cells (iPSC) and their EVs to suppress immune responses on the onset of sialadenitis in the NOD mouse model of Sjögren's Syndrome (SS) has been shown. Furthermore, it been found that iPSC-derived EVs prevented lymphocyte infiltration in SMGs and production of autoantibodies, however, the MVs efficacy was lower than the cells [138].

Conclusion

A number of studies have been shown that MSCs possess immunosuppressive capacity. Remarkably, these findings turned scientist's attention to utilize MSC-based therapy for autoimmune diseases. Although a few clinical studies dealing with the potential application of MSCs for treatment have shown encouraging results, it has not still been led to a conventional therapy.

Moreover, tumorigenic potential of MSCs is a major concern. Interestingly, recent findings have indicated that the immunosuppressive properties of MSCs are because of, at least in part, to extracellular vesicle (EV) secretion. In other words, MSC-derived EVs can be utilized as a cell-free therapeutic alternative. Despite the positive results, based of preclinical and clinical studies, in which MSC-derived EVs have been used as a novel modality for treatment of autoimmune disorders, they are still in developing and research stages. It is noteworthy that EVs are classified as biological drugs and considered as advanced therapy medicinal products ATMPs. Therefore, They have own GMP regulation that differ with MSCs. However, with regard to storage and industrial-scale production, it seems more reasonable than MSCs. On the other hand, due to promising initial results

for clinical utilization of MSCs in some autoimmune diseases such as Lupus Erythematous (LE), GVHD, Sjögren syndrome (SS), SLE, Crohn's Disease and MS, it would be reasonable to expect that MSC-derived EVs exert same beneficial effects even more advantages. Overall, MSC-derived EVs might be an emerging and new modality for treatment of autoimmune diseases but they are at first steps on the long route to clinical application and require further and comprehensive investigations.

Acknowledgements Part of this study was supported by Guilan University of Medical Sciences (Grant No: IR.GUMS.REC.1396.343).

Compliance with ethical standards

Conflict of interest The authors declare no potential conflicts of interest.

References

1. Wang L, Wang FS, Gershwin ME (2015) Human autoimmune diseases: a comprehensive update. J Intern Med 278(4):369–395
2. Ray S, Sonthalia N, Kundu S, Ganguly S (2012) Autoimmune disorders: an overview of molecular and cellular basis in today's perspective. J Clin Cell Immunol S 10:003
3. Abbas AK, Lichtman AH, Pillai S (2014) Cellular and molecular immunology E-book: Elsevier Health Sciences
4. Jancar S, Crespo MS (2005) Immune complex-mediated tissue injury: a multistep paradigm. Trends Immunol 26(1):48–55
5. Muñoz LE, Lauber K, Schiller M, Manfredi AA, Herrmann M (2010) The role of defective clearance of apoptotic cells in systemic autoimmunity. Nat Rev Rheumatol 6(5):280
6. Roeleveld DM, Koenders MI (2015) The role of the Th17 cytokines IL-17 and IL-22 in rheumatoid arthritis pathogenesis and developments in cytokine immunotherapy. Cytokine 74(1):101–107
7. Zhang H-L, Zheng X-Y, Zhu J (2013) Th1/Th2/Th17/Treg cytokines in Guillain–Barré syndrome and experimental autoimmune neuritis. Cytokine Growth Factor Rev 24(5):443–453
8. Li Y-F, Zhang S-X, Ma X-W, Xue Y-L, Gao C, Li X-Y (2017) Levels of peripheral Th17 cells and serum Th17-related cytokines in patients with multiple sclerosis: a meta-analysis. Multiple Scler Relat Disord 18:20–25
9. Nicoletti F, Créange A, Orlikowski D, Bolgert F, Mangano K, Metz C et al (2005) Macrophage migration inhibitory factor (MIF) seems crucially involved in Guillain–Barré syndrome and experimental allergic neuritis. J Neuroimmunol 168(1–2):168–174
10. Benedek G, Meza-Romero R, Jordan K, Zhang Y, Nguyen H, Kent G et al (2017) MIF and D-DT are potential disease severity modifiers in male MS subjects. Proc Natl Acad Sci 114(40):E8421–E9
11. Fagone P, Mazzon E, Cavalli E, Bramanti A, Petralia MC, Mangano K et al (2018) Contribution of the macrophage migration inhibitory factor superfamily of cytokines in the pathogenesis of preclinical and human multiple sclerosis: in silico and in vivo evidences. J Neuroimmunol 322:46–56
12. Karo-Atar D, Bitton A, Benhar I, Munitz A (2018) Therapeutic targeting of the interleukin-4/interleukin-13 signaling pathway: in allergy and beyond. BioDrugs 32:1–20
13. Fagone P, Mangano K, Pesce A, Portale TR, Puleo S, Nicoletti F (2016) Emerging therapeutic targets for the treatment of hepatic fibrosis. Drug Discov Today 21(2):369–375
14. Barcellini W, Rizzardi G, Borghi M, Nicoletti F, Fain C, Del Papa N et al (1996) In vitro type-1 and type-2 cytokine production in systemic lupus erythematosus: lack of relationship with clinical disease activity. Lupus 5(2):139–145
15. Nicoletti F, Di Marco R, Patti F, Reggio E, Nicoletti A, Zaccone P et al (1998) Blood levels of transforming growth factor-beta 1 (TGF-β1) are elevated in both relapsing remitting and chronic progressive multiple sclerosis (MS) patients and are further augmented by treatment with interferon-beta 1b (IFN-β1b). Clin Exp Immunol 113(1):96–99
16. Dujmovic I, Mangano K, Pekmezovic T, Quattrocchi C, Mesaros S, Stojsavljevic N et al (2009) The analysis of IL-1 beta and its naturally occurring inhibitors in multiple sclerosis: the elevation of IL-1 receptor antagonist and IL-1 receptor type II after steroid therapy. J Neuroimmunol 207(1–2):101–106
17. Nadkarni S, Mauri C, Ehrenstein MR (2007) Anti-TNF-α therapy induces a distinct regulatory T cell population in patients with rheumatoid arthritis via TGF-β. J Exp Med 204(1):33–39
18. Wu Q, Wang Q, Mao G, Dowling CA, Lundy SK, Mao-Draayer Y (2017) Dimethyl fumarate selectively reduces memory T cells and shifts the balance between Th1/Th17 and Th2 in multiple sclerosis patients. J Immunol. https://doi.org/10.4049/jimmunol.1601532
19. Lai Y, Dong C (2015) Therapeutic antibodies that target inflammatory cytokines in autoimmune diseases. Int Immunol 28(4):181–188
20. Fragoulis GE, Siebert S, McInnes IB (2016) Therapeutic targeting of IL-17 and IL-23 cytokines in immune-mediated diseases. Ann Rev Med 67:337–353
21. Scharl M, Vavricka R, Rogler G (2013) New anti-cytokines for IBD: what is in the pipeline? Curr Drug Targets 14(12):1405–1420
22. Ramos-Casals M, Diaz-Lagares C, Cuadrado M-J, Khamashta MA, Group BS (2010) Autoimmune diseases induced by biological agents: a double-edged sword? Autoimmun Rev 9(3):188–193
23. Zintzaras E, Voulgarelis M, Moutsopoulos HM (2005) The risk of lymphoma development in autoimmune diseases: a meta-analysis. Arch Intern Med 165(20):2337–2344
24. Pérez-De-Lis M, Retamozo S, Flores-Chávez A, Kostov B, Perez-Alvarez R, Brito-Zerón P et al (2017) Autoimmune diseases induced by biological agents. A review of 12,731 cases (BIOGEAS Registry). Expert Opin Drug Saf 16(11):1255–1271
25. Kalden JR, Schulze-Koops H (2017) Immunogenicity and loss of response to TNF inhibitors: implications for rheumatoid arthritis treatment. Nat Rev Rheumatol 13(12):707
26. Tyndall A (2011) Successes and failures of stem cell transplantation in autoimmune diseases. ASH Educ Program Book 2011(1):280–284
27. Del Fattore A, Luciano R, Pascucci L, Goffredo BM, Giorda E, Scapaticci M et al (2015) Immunoregulatory effects of mesenchymal stem cell-derived extracellular vesicles on T lymphocytes. Cell Transplant 24(12):2615–2627
28. Castro-Manrreza ME, Montesinos JJ (2015) Immunoregulation by mesenchymal stem cells: biological aspects and clinical applications. J Immunol Res. https://doi.org/10.1155/2015/394917
29. Blanco B, Herrero-Sánchez MdC, Rodríguez-Serrano C, García-Martínez ML, Blanco JF, Muntión S et al (2016) Immunomodulatory effects of bone marrow versus adipose tissue-derived mesenchymal stromal cells on NK cells: implications in the transplantation setting. Eur J Haematol 97(6):528–537
30. Amiri F, Jahanian-Najafabadi A, Roudkenar MH (2015) In vitro augmentation of mesenchymal stem cells viability in stressful microenvironments. Cell Stress Chaperones 20(2):237–251

31. Roushandeh AM, Bahadori M, Roudkenar MH (2017) Mesenchymal stem cell-based therapy as a new horizon for kidney injuries. Arch Med Res 48(2):133–146
32. Fontaine MJ, Shih H, Schäfer R, Pittenger MF (2016) Unraveling the mesenchymal stromal cells' paracrine immunomodulatory effects. Transfus Med Rev 30(1):37–43
33. Biancone L, Bruno S, Deregibus MC, Tetta C, Camussi G (2012) Therapeutic potential of mesenchymal stem cell-derived microvesicles. Nephrol Dial Transplant 27(8):3037–3042
34. Baglio SR, Pegtel DM, Baldini N (2012) Mesenchymal stem cell secreted vesicles provide novel opportunities in (stem) cell-free therapy. Front Physiol 3:359
35. Chen TS, Lai RC, Lee MM, Choo ABH, Lee CN, Lim SK (2009) Mesenchymal stem cell secretes microparticles enriched in pre-microRNAs. Nucleic Acids Res 38(1):215–224
36. Abbasi-Malati Z, Roushandeh AM, Kuwahara Y, Roudkenar MH (2018) Mesenchymal stem cells on horizon: a new arsenal of therapeutic agents. Stem Cell Rev Rep 14:484–499
37. Bassi ÊJ, de Almeida DC, Moraes-Vieira PMM, Câmara NOS (2012) Exploring the role of soluble factors associated with immune regulatory properties of mesenchymal stem cells. Stem Cell Rev Rep 8(2):329–342
38. Vianello F, Dazzi F (2008) Mesenchymal stem cells for graft-versus-host disease: a double edged sword? Leukemia 22(3):463-465
39. Halabian R, Tehrani HA, Jahanian-Najafabadi A, Roudkenar MH (2013) Lipocalin-2-mediated upregulation of various antioxidants and growth factors protects bone marrow-derived mesenchymal stem cells against unfavorable microenvironments. Cell Stress Chaperones 18(6):785–800
40. Kiani AA, Kazemi A, Halabian R, Mohammadipour M, Jahanian-Najafabadi A, Roudkenar MH (2013) HIF-1α confers resistance to induced stress in bone marrow-derived mesenchymal stem cells. Arch Med Res 44(3):185–193
41. Wong RS (2011) Mesenchymal stem cells: angels or demons? BioMed Res Int. https://doi.org/10.1155/2011/459510
42. Bianco P, Robey PG, Simmons PJ (2008) Mesenchymal stem cells: revisiting history, concepts, and assays. Cell Stem Cell 2(4):313–319
43. Short B, Brouard N, Driessen R, Simmons P (2001) Prospective isolation of stromal progenitor cells from mouse BM. Cytotherapy 3(5):407–408
44. Barry FP, Murphy JM (2004) Mesenchymal stem cells: clinical applications and biological characterization. Int J Biochem Cell Biol 36(4):568–584
45. Amiri F, Halabian R, Salimian M, Shokrgozar MA, Soleimani M, Jahanian-Najafabadi A et al (2014) Induction of multipotency in umbilical cord-derived mesenchymal stem cells cultivated under suspension conditions. Cell Stress Chaperones 19(5):657–666
46. Amiri F, Halabian R, Dehgan Harati M, Bahadori M, Mehdipour A, Mohammadi Roushandeh A et al (2015) Positive selection of Wharton's jelly-derived CD105 + cells by MACS technique and their subsequent cultivation under suspension culture condition: a simple, versatile culturing method to enhance the multipotentiality of mesenchymal stem cells. Hematology 20(4):208–216
47. Troyer DL, Weiss ML (2008) Concise review: Wharton's jelly-derived cells are a primitive stromal cell population. Stem Cells 26(3):591–599
48. Chamberlain G, Fox J, Ashton B, Middleton J (2007) Concise review: mesenchymal stem cells: their phenotype, differentiation capacity, immunological features, and potential for homing. Stem Cells 25(11):2739–2749
49. Karussis D, Karageorgiou C, Vaknin-Dembinsky A, Gowda-Kurkalli B, Gomori JM, Kassis I et al (2010) Safety and immunological effects of mesenchymal stem cell transplantation in patients with multiple sclerosis and amyotrophic lateral sclerosis. Arch Neurol 67(10):1187–1194
50. Abdi R, Fiorina P, Adra CN, Atkinson M, Sayegh MH (2008) Immunomodulation by mesenchymal stem cells: a potential therapeutic strategy for type 1 diabetes. Diabetes 57(7):1759–1767
51. Le Blanc K, Ringden O (2007) Immunomodulation by mesenchymal stem cells and clinical experience. J Intern Med 262(5):509–525
52. Ghannam S, Bouffi C, Djouad F, Jorgensen C, Noël D (2010) Immunosuppression by mesenchymal stem cells: mechanisms and clinical applications. Stem Cell Res Ther 1(1):2
53. Klyushnenkova E, Mosca JD, Zernetkina V, Majumdar MK, Beggs KJ, Simonetti DW et al (2005) T cell responses to allogeneic human mesenchymal stem cells: immunogenicity, tolerance, and suppression. J Biomed Sci 12(1):47–57
54. Bradley JA, Bolton EM, Pedersen RA (2002) Stem cell medicine encounters the immune system. Nat Rev Immunol 2(11):859
55. Götherström C (2007) Immunomodulation by multipotent mesenchymal stromal cells. Transplantation 84(1):S35–S37
56. De Miguel P, Fuentes-Julian M, Blazquez-Martinez S, Pascual C AY, Aller A, Arias M et al (2012) Immunosuppressive properties of mesenchymal stem cells: advances and applications. Curr Mol Med 12(5):574–591
57. Aggarwal S, Pittenger MF (2005) Human mesenchymal stem cells modulate allogeneic immune cell responses. Blood 105(4):1815–1822
58. Kyurkchiev D, Bochev I, Ivanova-Todorova E, Mourdjeva M, Oreshkova T, Belemezova K et al (2014) Secretion of immunoregulatory cytokines by mesenchymal stem cells. World J Stem Cells 6(5):552
59. Castro-Manrreza ME (2016) Participation of mesenchymal stem cells in the regulation of immune response and cancer development. Boletín Médico Del Hospital Infantil de México (English Edition) 73(6):380–387
60. Le Blanc K, Tammik L, Sundberg B, Haynesworth S, Ringden O (2003) Mesenchymal stem cells inhibit and stimulate mixed lymphocyte cultures and mitogenic responses independently of the major histocompatibility complex. Scand J Immunol 57(1):11–20
61. Krampera M, Cosmi L, Angeli R, Pasini A, Liotta F, Andreini A et al (2006) Role for interferon-γ in the immunomodulatory activity of human bone marrow mesenchymal stem cells. Stem Cells 24(2):386–398
62. Glennie S, Soeiro I, Dyson PJ, Lam EW-F, Dazzi F (2005) Bone marrow mesenchymal stem cells induce division arrest anergy of activated T cells. Blood 105(7):2821–2827
63. Saldanha-Araujo F, Ferreira FI, Palma PV, Araujo AG, Queiroz RH, Covas DT et al (2011) Mesenchymal stromal cells up-regulate CD39 and increase adenosine production to suppress activated T-lymphocytes. Stem Cell Res 7(1):66–74
64. Lee H-J, Kim S-N, Jeon M-S, Yi T, Song SU (2017) ICOSL expression in human bone marrow-derived mesenchymal stem cells promotes induction of regulatory T cells. Sci Rep 7:44486
65. Ko JH, Lee HJ, Jeong HJ, Kim MK, Wee WR, Yoon S-o et al (2016) Mesenchymal stem/stromal cells precondition lung monocytes/macrophages to produce tolerance against allo-and autoimmunity in the eye. Proc Natl Acad Sci 113(1):158–163
66. Yan L, Zheng D, Xu R (2018) Critical role of TNF signaling in mesenchymal stem cell-based therapy for autoimmune and inflammatory diseases. Front Immunol 9:1658
67. Angulski AB, Capriglione LG, Batista M, Marcon BH, Senegaglia AC, Stimamiglio MA et al (2017) The protein content of extracellular vesicles derived from expanded human umbilical cord blood-derived CD133+ and human bone marrow-derived mesenchymal stem cells partially explains why both sources are advantageous for regenerative medicine. Stem Cell Rev Rep 13(2):244–257

68. Sagini K, Costanzi E, Emiliani C, Buratta S, Urbanelli L (2018) Extracellular vesicles as conveyors of membrane-derived bioactive lipids in immune system. Int J Mol Sci 19(4):1227
69. Blazquez R, Sanchez-Margallo FM, de la Rosa O, Dalemans W, Álvarez V, Tarazona R et al (2014) Immunomodulatory potential of human adipose mesenchymal stem cells derived exosomes on in vitro stimulated T cells. Front Immunol 5:556
70. de Araújo Farias V, Carrillo-Gálvez AB, Martín F, Anderson P (2018) TGF-β and mesenchymal stromal cells in regenerative medicine, autoimmunity and cancer. Cytokine Growth Factor Rev 43:25–37
71. Gebler A, Zabel O, Seliger B (2012) The immunomodulatory capacity of mesenchymal stem cells. Trends Mol Med 18(2):128–134
72. Uccelli A, Moretta L, Pistoia V (2008) Mesenchymal stem cells in health and disease. Nat Rev Immunol 8(9):726
73. Ivanova-Todorova E, Bochev I, Mourdjeva M, Dimitrov R, Bukarev D, Kyurkchiev S et al (2009) Adipose tissue-derived mesenchymal stem cells are more potent suppressors of dendritic cells differentiation compared to bone marrow-derived mesenchymal stem cells. Immunol Lett 126(1–2):37–42
74. Nauta AJ, Kruisselbrink AB, Lurvink E, Willemze R, Fibbe WE (2006) Mesenchymal stem cells inhibit generation and function of both CD34+-derived and monocyte-derived dendritic cells. J Immunol 177(4):2080–2087
75. Liu W-h, Liu J-j, Wu J, Zhang L-l, Liu F, Yin L et al (2013) Novel mechanism of inhibition of dendritic cells maturation by mesenchymal stem cells via interleukin-10 and the JAK1/STAT3 signaling pathway. PLoS ONE 8(1):e55487
76. Sotiropoulou PA, Perez SA, Gritzapis AD, Baxevanis CN, Papamichail M (2006) Interactions between human mesenchymal stem cells and natural killer cells. Stem Cells 24(1):74–85
77. Raffaghello L, Bianchi G, Bertolotto M, Montecucco F, Busca A, Dallegri F et al (2008) Human mesenchymal stem cells inhibit neutrophil apoptosis: a model for neutrophil preservation in the bone marrow niche. Stem Cells 26(1):151–162
78. Zhao Q, Ren H, Han Z (2016) Mesenchymal stem cells: immunomodulatory capability and clinical potential in immune diseases. J Cell Immunother 2(1):3–20
79. He M, Shi X, Yang M, Yang T, Li T, Chen J (2019) Mesenchymal stem cells-derived IL-6 activates AMPK/mTOR signaling to inhibit the proliferation of reactive astrocytes induced by hypoxic-ischemic brain damage. Exp Neurol 311:15–32
80. Mammana S, Bramanti P, Mazzon E, Cavalli E, Basile MS, Fagone P et al (2018) Preclinical evaluation of the PI3K/Akt/mTOR pathway in animal models of multiple sclerosis. Oncotarget 9(9):8263
81. Donia M, Mangano K, Amoroso A, Mazzarino MC, Imbesi R, Castrogiovanni P et al (2009) Treatment with rapamycin ameliorates clinical and histological signs of protracted relapsing experimental allergic encephalomyelitis in Dark Agouti rats and induces expansion of peripheral CD4+ CD25+ Foxp3+ regulatory T cells. J Autoimmun 33(2):135–140
82. Faustman D, Davis M (2010) TNF receptor 2 pathway: drug target for autoimmune diseases. Nat Rev Drug Discov 9(6):482
83. Zappia E, Casazza S, Pedemonte E, Benvenuto F, Bonanni I, Gerdoni E et al (2005) Mesenchymal stem cells ameliorate experimental autoimmune encephalomyelitis inducing T-cell anergy. Blood 106(5):1755–1761
84. Djouad F, Fritz V, Apparailly F, Louis-Plence P, Bony C, Sany J et al (2005) Reversal of the immunosuppressive properties of mesenchymal stem cells by tumor necrosis factor α in collagen-induced arthritis. Arthritis Rheum 52(5):1595–1603
85. González MA, Gonzalez-Rey E, Rico L, Büscher D, Delgado M (2009) Treatment of experimental arthritis by inducing immune tolerance with human adipose-derived mesenchymal stem cells. Arthritis Rheum 60(4):1006–1019
86. Choi JJ, Yoo SA, Park SJ, Kang YJ, Kim WU, Oh IH et al (2008) Mesenchymal stem cells overexpressing interleukin-10 attenuate collagen-induced arthritis in mice. Clin Exp Immunol 153(2):269–276
87. Villatoro AJ, Fernández V, Claros S, Rico-Llanos GA, Becerra J, Andrades JA (2015) Use of adipose-derived mesenchymal stem cells in keratoconjunctivitis sicca in a canine model. BioMed Res Int. https://doi.org/10.1155/2015/527926
88. Bassi ÊJ, Moraes-Vieira PM, Sá CSM, Almeida DC, Vieira LM, Cunha CS et al (2012) Immune regulatory properties of allogeneic adipose-derived mesenchymal stem cells in the treatment of experimental autoimmune diabetes. Diabetes. https://doi.org/10.2337/db11-0844
89. Rafei M, Campeau PM, Aguilar-Mahecha A, Buchanan M, Williams P, Birman E et al (2009) Mesenchymal stromal cells ameliorate experimental autoimmune encephalomyelitis by inhibiting CD4 Th17 T cells in a CC chemokine ligand 2-dependent manner. J Immunol 182(10):5994–6002
90. Jang E, Jeong M, Kim S, Jang K, Kang B-K, Lee DY et al (2016) Infusion of human bone marrow-derived mesenchymal stem cells alleviates autoimmune nephritis in a lupus model by suppressing follicular helper T-cell development. Cell Transplant 25(1):1–15
91. Youd M, Blickarz C, Woodworth L, Touzjian T, Edling A, Tedstone J et al (2010) Allogeneic mesenchymal stem cells do not protect NZB × NZW F1 mice from developing lupus disease. Clin Exp Immunol 161(1):176–186
92. Linero I, Chaparro O (2014) Paracrine effect of mesenchymal stem cells derived from human adipose tissue in bone regeneration. PLoS ONE 9(9):e107001
93. Yu B, Zhang X, Li X (2014) Exosomes derived from mesenchymal stem cells. Int J Mol Sci 15(3):4142–4157
94. Baraniak PR, McDevitt TC (2010) Stem cell paracrine actions and tissue regeneration. Regenerat Med 5(1):121–143
95. Shimada Y, Minna JD (2017) Exosome mediated phenotypic changes in lung cancer pathophysiology. Transl Cancer Res 6(S6):S1040–S1042
96. Simons M, Raposo G (2009) Exosomes-vesicular carriers for intercellular communication. Curr Opin Cell Biol 21(4):575–581
97. Rad F, Pourfathollah AA, Yari F, Mohammadi S, Kheirandish M (2016) Microvesicles preparation from mesenchymal stem cells. Med J IR Iran 30:398
98. Nassar W, El-Ansary M, Aziz MA, El-Hakim E (2015) Extracellular vesicles: fundamentals and clinical relevance. Egypt J Intern Med 27(1):1
99. Pan B-T, Johnstone RM (1983) Fate of the transferrin receptor during maturation of sheep reticulocytes in vitro: selective externalization of the receptor. Cell 33(3):967–978
100. Rani S, Ryan AE, Griffin MD, Ritter T (2015) Mesenchymal stem cell-derived extracellular vesicles: toward cell-free therapeutic applications. Mol Ther 23(5):812–823
101. Szatanek R, Baran J, Siedlar M, Baj-Krzyworzeka M (2015) Isolation of extracellular vesicles: determining the correct approach. Int J Mol Med 36(1):11–17
102. Jeppesen DK, Hvam ML, Primdahl-Bengtson B, Boysen AT, Whitehead B, Dyrskjøt L et al (2014) Comparative analysis of discrete exosome fractions obtained by differential centrifugation. J Extracell Vesicles 3(1):25011
103. Van der Pol E, Böing AN, Harrison P, Sturk A, Nieuwland R (2012) Classification, functions, and clinical relevance of extracellular vesicles. Pharmacol Rev 64(3):676–705
104. Simpson RJ, Kalra H, Mathivanan S (2012) ExoCarta as a resource for exosomal research. J Extracell Vesicles 1(1):18374
105. Raposo G, Stoorvogel W (2013) Extracellular vesicles: exosomes, microvesicles, and friends. J Cell Biol 200(4):373–383

106. Beer KB, Wehman AM (2017) Mechanisms and functions of extracellular vesicle release in vivo—what we can learn from flies and worms. Cell Adhes Migr 11(2):135–150
107. Tricarico C, Clancy J, D'Souza-Schorey C (2017) Biology and biogenesis of shed microvesicles. Small GTPases 8(4):220–232
108. Katsuda T, Kosaka N, Takeshita F, Ochiya T (2013) The therapeutic potential of mesenchymal stem cell-derived extracellular vesicles. Proteomics 13(10–11):1637–1653
109. Collino F, Deregibus MC, Bruno S, Sterpone L, Aghemo G, Viltono L et al (2010) Microvesicles derived from adult human bone marrow and tissue specific mesenchymal stem cells shuttle selected pattern of miRNAs. PLoS ONE 5(7):e11803
110. Bruno S, Collino F, Deregibus MC, Grange C, Tetta C, Camussi G (2012) Microvesicles derived from human bone marrow mesenchymal stem cells inhibit tumor growth. Stem Cells Dev 22(5):758–771
111. Bruno S, Grange C, Deregibus MC, Calogero RA, Saviozzi S, Collino F et al (2009) Mesenchymal stem cell-derived microvesicles protect against acute tubular injury. J Am Soc Nephrol 20(5):1053–1067
112. Skalnikova HK (2013) Proteomic techniques for characterisation of mesenchymal stem cell secretome. Biochimie 95(12):2196–2211
113. Kim H-S, Choi D-Y, Yun SJ, Choi S-M, Kang JW, Jung JW et al (2011) Proteomic analysis of microvesicles derived from human mesenchymal stem cells. J Proteome Res 11(2):839–849
114. Zhang H-C, Liu X-B, Huang S, Bi X-Y, Wang H-X, Xie L-X et al (2012) Microvesicles derived from human umbilical cord mesenchymal stem cells stimulated by hypoxia promote angiogenesis both in vitro and in vivo. Stem Cells Dev 21(18):3289–3297
115. Park C, Huang JZ, Ji JX, Ding Y (2013) Segmentation, inference and classification of partially overlapping nanoparticles. IEEE Trans Pattern Anal Mach Intell 35(3):1–1
116. Yáñez-Mó M, Siljander PR-M, Andreu Z, Bedina Zavec A, Borràs FE, Buzas EI et al (2015) Biological properties of extracellular vesicles and their physiological functions. J Extracell Vesicles 4(1):27066
117. Kalra H, Drummen GP, Mathivanan S (2016) Focus on extracellular vesicles: introducing the next small big thing. Int J Mol Sci 17(2):170
118. Lin J, Li J, Huang B, Liu J, Chen X, Chen X-M et al (2015) Exosomes: novel biomarkers for clinical diagnosis. Sci World J. https://doi.org/10.1155/2015/657086
119. Ferguson SW, Nguyen J (2016) Exosomes as therapeutics: the implications of molecular composition and exosomal heterogeneity. J Controlled Release 228:179–190
120. Valadi H, Ekström K, Bossios A, Sjöstrand M, Lee JJ, Lötvall JO (2007) Exosome-mediated transfer of mRNAs and microRNAs is a novel mechanism of genetic exchange between cells. Nat Cell Biol 9(6):654
121. Ratajczak MZ, Ratajczak J (2016) Horizontal transfer of RNA and proteins between cells by extracellular microvesicles: 14 years later. Clin Transl Med 5(1):7
122. Quesenberry PJ, Aliotta J, Deregibus MC, Camussi G (2015) Role of extracellular RNA-carrying vesicles in cell differentiation and reprogramming. Stem Cell Res Ther 6(1):153
123. Quesenberry PJ, Goldberg LR, Aliotta JM, Dooner MS, Pereira MG, Wen S et al (2014) Cellular phenotype and extracellular vesicles: basic and clinical considerations. Stem Cells Dev 23(13):1429–1436
124. Nawaz M, Fatima F, Vallabhaneni KC, Penfornis P, Valadi H, Ekström K et al (2016) Extracellular vesicles: evolving factors in stem cell biology. Stem Cells Int. https://doi.org/10.1155/2016/1073140
125. Nawaz M, Fatima F (2017) Extracellular vesicles, tunneling nanotubes, and cellular interplay: synergies and missing links. Front Mol Biosci 4:50
126. Ti D, Hao H, Tong C, Liu J, Dong L, Zheng J et al (2015) LPS-preconditioned mesenchymal stromal cells modify macrophage polarization for resolution of chronic inflammation via exosome-shuttled let-7b. J Transl Med 13(1):308
127. Ti D, Hao H, Fu X, Han W (2016) Mesenchymal stem cells-derived exosomal microRNAs contribute to wound inflammation. Sci China Life Sci 59(12):1305–1312
128. Di Rocco G, Baldari S, Toietta G (2016) Towards therapeutic delivery of extracellular vesicles: strategies for in vivo tracking and biodistribution analysis. Stem Cells Int. https://doi.org/10.1155/2016/5029619
129. Wiklander OP, Nordin JZ, O'Loughlin A, Gustafsson Y, Corso G, Mäger I et al (2015) Extracellular vesicle in vivo biodistribution is determined by cell source, route of administration and targeting. J Extracell Vesicles 4(1):26316
130. Grange C, Tapparo M, Bruno S, Chatterjee D, Quesenberry PJ, Tetta C et al (2014) Biodistribution of mesenchymal stem cell-derived extracellular vesicles in a model of acute kidney injury monitored by optical imaging. Int J Mol Med 33(5):1055–1063
131. Budoni M, Fierabracci A, Luciano R, Petrini S, Di Ciommo V, Muraca M (2013) The immunosuppressive effect of mesenchymal stromal cells on B lymphocytes is mediated by membrane vesicles. Cell Transpl 22(2):369–379
132. Henao Agudelo JS, Braga TT, Amano MT, Cenedeze MA, Cavinato RA, Peixoto-Santos AR et al (2017) Mesenchymal stromal cell-derived microvesicles regulate an internal pro-inflammatory program in activated macrophages. Front Immunol 8:881
133. Shigemoto-Kuroda T, Oh JY, Kim D-k, Jeong HJ, Park SY, Lee HJ et al (2017) MSC-derived extracellular vesicles attenuate immune responses in two autoimmune murine models: type 1 diabetes and uveoretinitis. Stem Cell Rep 8(5):1214–1225
134. Cosenza S, Toupet K, Maumus M, Luz-Crawford P, Blanc-Brude O, Jorgensen C et al (2018) Mesenchymal stem cells-derived exosomes are more immunosuppressive than microparticles in inflammatory arthritis. Theranostics 8(5):1399
135. Kordelas L, Rebmann V, Ludwig A, Radtke S, Ruesing J, Doeppner T et al (2014) MSC-derived exosomes: a novel tool to treat therapy-refractory graft-versus-host disease. Leukemia 28(4):970
136. Favaro E, Carpanetto A, Caorsi C, Giovarelli M, Angelini C, Cavallo-Perin P et al (2016) Human mesenchymal stem cells and derived extracellular vesicles induce regulatory dendritic cells in type 1 diabetic patients. Diabetologia 59(2):325–333
137. Sharma J, Hampton JM, Valiente GR, Wada T, Steigelman H, Young MC et al (2017) Therapeutic development of mesenchymal stem cells or their extracellular vesicles to inhibit autoimmune-mediated inflammatory processes in systemic lupus erythematosus. Front Immunol 8:526
138. Hai B, Shigemoto-Kuroda T, Zhao Q, Lee RH, Liu F (2018) Inhibitory effects of iPSC-MSCs and their extracellular vesicles on the onset of sialadenitis in a mouse model of Sjögren's Syndrome. Stem Cells Int. https://doi.org/10.1155/2018/2092315
139. Soundara Rajan T, Giacoppo S, Diomede F, Bramanti P, Trubiani O, Mazzon E (2017) Human periodontal ligament stem cells secretome from multiple sclerosis patients suppresses NALP3 inflammasome activation in experimental autoimmune encephalomyelitis. Int J Immunopathol Pharmacol 30(3):238–252
140. Nojehdehi S, Soudi S, Hesampour A, Rasouli S, Soleimani M, Hashemi SM (2018) Immunomodulatory effects of mesenchymal stem cell-derived exosomes on experimental type-1 autoimmune diabetes. J Cell Biochem 119(11):9433–9443
141. Rajan TS, Giacoppo S, Diomede F, Ballerini P, Paolantonio M, Marchisio M et al (2016) The secretome of periodontal ligament

stem cells from MS patients protects against EAE. Sci Rep 6:38743
142. Laso-García F, Ramos-Cejudo J, Carrillo-Salinas FJ, Otero-Ortega L, Feliú A, Gómez-de Frutos M et al (2018) Therapeutic potential of extracellular vesicles derived from human mesenchymal stem cells in a model of progressive multiple sclerosis. PLoS ONE 13(9):e0202590
143. Chen Z, Wang H, Xia Y, Yan F, Lu Y (2018) Therapeutic potential of mesenchymal cell-derived miRNA-150-5p-expressing exosomes in rheumatoid arthritis mediated by the modulation of MMP14 and VEGF. J Immunol 201(8):2472–2482
144. Zhu L, Huang X, Yu W, Chen H, Chen Y, Dai Y (2018) Transplantation of adipose tissue-derived stem cell-derived exosomes ameliorates erectile function in diabetic rats. Andrologia 50(2):e12871
145. Mokarizadeh A, Delirezh N, Morshedi A, Mosayebi G, Farshid A-A, Mardani K (2012) Microvesicles derived from mesenchymal stem cells: potent organelles for induction of tolerogenic signaling. Immunol Lett 147(1–2):47–54
146. Jacquelin S, Licata F, Dorgham K, Hermand P, Poupel L, Guyon E et al (2013) CX3CR1 reduces Ly6Chigh-monocyte motility within, and release from the bone marrow after chemotherapy in mice. Blood. https://doi.org/10.1182/blood-2013-01-480749
147. Hidalgo-Garcia L, Galvez J, Rodriguez-Cabezas ME, Anderson PO (2018) Can a conversation between mesenchymal stromal cells and macrophages solve the crisis in the inflamed intestine? Front Pharmacol 9:179
148. Jaimes Y, Naaldijk Y, Wenk K, Leovsky C, Emmrich F (2017) Mesenchymal stem cell-derived microvesicles modulate lipopolysaccharides-induced inflammatory responses to microglia cells. Stem Cells 35(3):812–823
149. Bruno S, Deregibus MC, Camussi G (2015) The secretome of mesenchymal stromal cells: role of extracellular vesicles in immunomodulation. Immunol Lett 168(2):154–158
150. Favaro E, Deregibus M, Camussi E, Granata R, Ghigo E, Cavallo PP et al (2012) Mesenchymal stem cells-derived microvesicles modulate cellular immune response to islet antigen GAD in type 1 diabetes. 15th International & 14th European Congress of Endocrinology; BioScientifica
151. Tamura R, Uemoto S, Tabata Y (2016) Immunosuppressive effect of mesenchymal stem cell-derived exosomes on a concanavalin A-induced liver injury model. Inflamm Regenerat 36(1):26
152. Zhang B, Yin Y, Lai RC, Tan SS, Choo ABH, Lim SK (2013) Mesenchymal stem cells secrete immunologically active exosomes. Stem Cells Dev 23(11):1233–1244
153. Cosenza S, Ruiz M, Maumus M, Jorgensen C, Noël D (2017) Pathogenic or therapeutic extracellular vesicles in rheumatic diseases: role of mesenchymal stem cell-derived vesicles. Int J Mol Sci 18(4):889
154. Perez-Hernandez J, Redon J, Cortes R (2017) Extracellular vesicles as therapeutic agents in systemic lupus erythematosus. Int J Mol Sci 18(4):717
155. Bai L, Shao H, Wang H, Zhang Z, Su C, Dong L et al (2017) Effects of mesenchymal stem cell-derived exosomes on experimental autoimmune uveitis. Sci Rep 7(1):4323