Cell Transplantation
Volume 32: 1–14

DOI: 10.1177/09636897231207194
journals.sagepub.com/home/cll
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Mesenchymal Stem Cell–Derived Extracellular Vesicles: New Soldiers in the War on Immune-Mediated Diseases

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Abstract

Inflammatory diseases are a group of debilitating disorders with varying degrees of long-lasting functional impairment of targeted system. New therapeutic agents that will attenuate on-going inflammation and, at the same time, promote regeneration of injured organ are urgently needed for the treatment of autoimmune and inflammatory disorders. During the last decade numerous studies have demonstrated that crucial therapeutic benefits of mesenchymal stem cells (MSCs) in inflammatory diseases are based on the effects of MSC-produced paracrine mediators and not on the activity of engrafted cells themselves. Thus, to overcome the limitations of stem cell transplantation, MSC-derived extracellular vesicles (MSC-EVs) have been rigorously investigated, as a promising cell-free pharmaceutical component. In this review, we focus on the mechanisms of MSC-EV covering the current knowledge on their potential therapeutic applications for immune-mediated diseases.

Keywords

mesenchymal stem cells, exosomes, inflammation, immune-mediated disease, cell-free therapy

Introduction

Inflammatory diseases are a group of debilitating disorders with varying degrees of long-lasting functional impairment of targeted system[1]. Epidemiological data showed a persistent increase in the incidence of this human diseases during the last 20 years with an estimated incidence of 80 per 10^5 person-years[2,3]. A detailed understanding of molecular mechanisms involved in their pathophysiology led to the use of broad-acting immunosuppressive medications, as a mainstream treatment option[4]. Corticosteroids and anti-cytokine/cytokine receptor monoclonal antibodies are very effective in patients with inflammatory disorders; however, their administration is associated with severe adverse effects due to global immune suppression[1,5]. Accordingly, new therapeutic agents that will attenuate on-going inflammation and, at the same time, promote regeneration of injured organ are urgently needed for the treatment of autoimmune and inflammatory diseases.

Due to their differentiation abilities, and capacity to produce variety of bioactive molecules, stem cells have raised tremendous expectations among the medical doctors, researchers, patients, and the general public as novel therapeutic agents in medicine. The most promising type of adult stem cells for clinical application is mesenchymal stem cells (MSCs). These cells can be isolated from nearly every tissue type in the adult or infant human body. Morphologically, MSCs are spindle-shaped, plastic-adherent cells which proliferate well *in vitro*[6]. Stem cell research community phenotypically characterized MSCs according to the expression of cluster of differentiation CD105, CD73, and CD90; lack of expression of hematopoietic and endothelial-specific antigens; and differentiation capacity toward the mesodermal lineage[6]. The most of lately published articles have demonstrated that undifferentiated MSCs possess the capacity to decrease inflammation, apoptosis, and fibrosis, while increase vasculogenesis and endogenous regeneration, making them an ideal candidate for the treatment of immune-mediated disorders[7].

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Submitted: April 21, 2023. Revised: September 11, 2023. Accepted: September 27, 2023.

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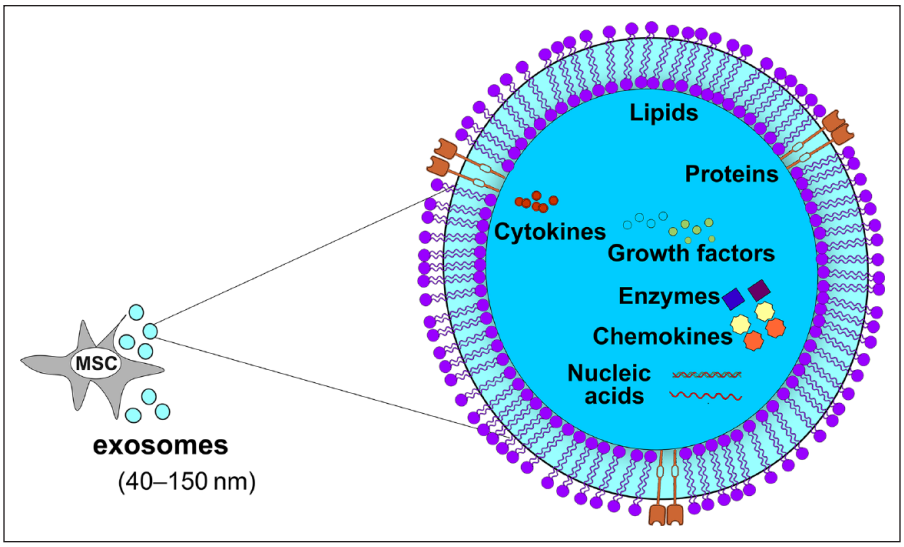

Figure 1. MSC-Exo biogenesis and its components. MSC-Exo are 40- to 150-nm-diameter vesicles with phospholipid bilayer membrane containing proteins, lipids, cytokines, growth factors, enzymes, chemokines, and nucleic acids. MSC-Exo packaged with broad range of different macromolecules may regulate fundamental biological processes. MSC: mesenchymal stem cell; MSC Exo: MSC-derived exosomes.

Intravenously transplanted MSCs, stimulated by damage-associated molecular patterns and alarmins released from injured cells, respond on overexpressed chemokines orchestrating cell migration to site of injury[8–10]. Despite the promising research data, the medical use of MSCs is restricted due to some practical limitations including reduced viability of engrafted cells in the injured tissue post-transplantation because of detrimental effects of increased level of reactive oxygen radicals (ROS) and inflammatory mediators and reduced availability of nutrients. Moreover, there are safety challenges regarding MSC-based therapy. The crucial obstacle is unwanted differentiation of administrated MSCs into undesirable cell type such as osteocyte and chondrocyte[11]. In addition to uncontrolled differentiation, MSCs are capable to inhibit anti-tumor immunity and stimulate neo-angiogenesis in tumor microenvironment, leading to cancer progression[12].

However, in the last few years broad range of studies have confirmed that main therapeutic effects of MSCs in immune-mediated disorders are based on the capacity of MSCs to secrete bioactive molecules and not on their progenitor properties[7]. Thus, to overcome the limitations of stem cell transplantation, MSC-derived secretome has been rigorously investigated, as a promising cell-free pharmaceutical component[7]. In this review, we focus on the mechanisms of MSC-derived extracellular vesicles (MSC-EVs) covering the current knowledge on their potential therapeutic applications for immune-mediated diseases.

Characteristics and Cargo of MSC-EVs

MSC-derived secretome consists of soluble proteins (growth factors, cytokines, and metabolites) and nano-sized biovesicles including microvesicles and exosomes[13]. MSC-derived exosomes (MSC-Exo) are 40- to 150-nm-diameter vesicles with endosomal origin, formed through the fusion of multivesicular bodies (MVB) with the cell membrane (Fig. 1). Exosome released into the extracellular compartment can be either internalized by target cells or transferred to distant tissues via biological fluids, where it regulates different physiological processes[14]. MSC-Exo have been successfully obtained from bone marrow (BM)-, umbilical cord-, amniotic fluid-, adipose tissue-, synovial membrane-, embryonic stem cell- and induced pluripotent stem cell-derived MSCs[15]. To improve yield and purity, MSC-Exo isolation methods are currently based on combination of physical (ultracentrifugation and ultrafiltration), chemical (immunoaffinity chromatography), and physical/chemical methods (size exclusion chromatography and precipitation)[16].

ExoCarta, a database that involves all the published and unpublished data about exosome content, provides a valuable knowledge for exosome characterization[17]. The analysis revealed that chemical structure of MSC-Exo not only mirrors the composition of the donor cell but also reflects their biological properties. Lipids present in two-layer membrane of these vesicles (cholesterol, sphingomyelin, ceramide, phosphatidylserine, and prostaglandins) play a key role in preserving vesicle shape but may also take part in some exosome functions[18,19]. MSC-Exo contain the evolutionarily conserved group of proteins commonly used as exosome markers such as tetraspanins (CD63, CD81, and CD9), heat-shock proteins (HSP60, HSP70, and HSP90), MVB biogenesis proteins (ALIX and TSG101), as well as proteins involved in adhesion, signaling, and membrane transport (Rab GTPase and flotillin)[20]. Moreover, MSC-Exo are the vehicle for delivering many different kinds of MSC-derived bioactive proteins (cytokines, growth factors, enzymes, and chemokines)

involved in regulation of fundamental biological processes, reflecting their cellular source. Immunomodulatory molecules such as transforming growth factor-beta 1 (TGF-β1), interleukin-6 (IL-6), IL-10, hepatocyte growth factor (HGF), vascular endothelial growth factor (VEGF), and matrix metalloproteinases, detected in MSC-Exo, affect activation, phenotype, and effector functions of innate and adaptive immune cells[21,22]. Cytokines can be found not only deposited inside exosomes, but also integrated in the exosomal membrane itself[23]. Besides, various types of nucleic acids including messenger RNA, transfer RNA, long noncoding RNAs, microRNAs, and mitochondrial DNA, packed inside the exosomes and protected from the external environment and degradation, have shown to perform immunomodulatory functions as well[24,25]. MicroRNA-155 (miR-155) and miR-146 found in MSC-Exo resolve chronic inflammation, autoimmunity, and fibrosis by changing protein synthesis at the posttranscriptional level in immune cells[26,27], while exosomal miR-23b, miR-451, miR-223, miR-24, miR-125b, miR-31, miR-214, and miR-122 modulate anti-tumor immune response in similar manner[28]. In addition to endocytosis by recipient cells, mechanisms responsible for MSC-Exo–immune cells interaction are receptor-mediated fusion of exosome and plasma membrane of target cells as well as a direct paracrine release of exosome cargoes after the disintegration of exosome membranes due to increased acidity[29]. Accordingly, MSC-Exo have an immunosuppressive capacity similar to that of MSCs and therefore they can be used as an alternative to stem cell transplantation and a relevant therapeutic option for inflammatory diseases[30,31]. Utilizing MSC-Exo as a therapy overcomes main safety issues which can arise after applying live cells such as unwanted differentiation, mutations, tumor formation, and immune rejection[7]. Thus, exosomes are safer and easier to control compared to MSC administration. Due to their nano-size diameter, MSC-Exo may reach capillary network in distant tissues after intravenous infusion, whereas MSCs are predominantly entrapped in the lungs after systemic delivery. In contrast to transplanted cells which die shortly, and MSC-derived soluble factors which are rapidly degraded, exosomes and their cargo are protected from degradation and quite stable *in vivo*[32]. Moreover, as an extremely stable nanovesicle, MSC-Exo are not affected by freezing–thawing and can be isolated and perfectly preserved at −80°C until application, overcoming the necessity of *ex vivo* large-scale, Good Manufacturing Practice (GMP)-compliant manufacturing of MSCs. Recent studies revealed that preconditioning of MSCs with cytokines [interferon gamma (IFN-γ), tumor necrosis factor alpha (TNF-α), IL-1β, IL-6, and TGF-β], biomolecules (lipopolysaccharides, nitric oxide, and melatonin), or hypoxia enhances the secretion of exosomes and improves their therapeutic efficacy. In particular, exosomes secreted from the primed MSCs are enriched in anti-inflammatory proteins and anti-inflammatory RNAs, suggesting that pre-conditioning methods can be utilized to maximize the immunosuppressive and regenerative potential of MSC-Exo in inflammatory diseases[7,16,32].

However, due to the lack of specific markers, current extracellular vesicle (EV) including "exosome" preparations is heterogenous with undetermined purity and undefined biogenesis origin, so the term "EV" instead of "exosomes" was recommended, unless the purity and/or biogenesis pathways are demonstrated. To create a broader consensus for more uniform characterization of EV, and to improve reliability and reproducibility of published EV results, the International Society for Extracellular Vesicles (ISEV) formulated minimal criteria for defining MSC-EV. First, ISEV members suggested detailed reporting about the source material and isolation methods used, as this impacts reproducibility of results. Second, they recommended detailed characterization of the protein content and quantification of proteins expected to be enriched in EV using western blot, flow cytometry, and mass spectrometry. In addition, they requested single-particle characterization by two complementary methods such as imaging by electron microscopy, atomic force microscopy, fluorescence microscopy and sizing with nano-tracking analysis or dynamic light scattering. Finally, functional analysis should include proper control samples, to demonstrate that the activity is predominantly associated with EV[33,34].

Accordingly, in this review article we summarized findings obtained in preclinical and clinical studies that demonstrated beneficent effects of MSC-EV in the treatment of inflammatory diseases. An extensive literature review was carried out across several databases (MEDLINE, EMBASE, Google Scholar, ClinicalTrials.gov), from 1990 to present. Keywords used in the selection were: "mesenchymal stem cells," "exosomes," "inflammation," "inflammatory bowel diseases," "acute hepatitis," "chronic liver injury," "cardiovascular diseases," and "diabetes mellitus." Eligible studies had to delineate molecular and cellular mechanisms involved in the MSC-EV–based therapy of immune-mediated diseases and their findings were analyzed in this review.

MSC-EVs for Cell-Free Therapies

MSC-EV–Mediated Attenuation of Acute and Chronic Liver Inflammation

It is well-known that the administration of MSCs in acute and chronic liver injury ameliorates the progress of these diseases. Most recently, we described molecular and cellular mechanisms involved in MSC-mediated attenuation of fulminant hepatitis and liver cirrhosis that is relied on the interaction between MSC's secretome and immune cells in the injured livers of mice[8,9,35].

Similar therapeutic effect *in vivo* was obtained when purified MSC-Exo were applied in liver diseases instead of MSC-conditioned medium. MSC-Exo isolated from different sources efficiently attenuated acute hepatitis as determined by decreased serum levels of transaminases and reduced mortality of experimental animals[36,37] (Fig. 2). In accordance with the biochemical analysis, MSC-Exo significantly attenuated production of proinflammatory cytokines

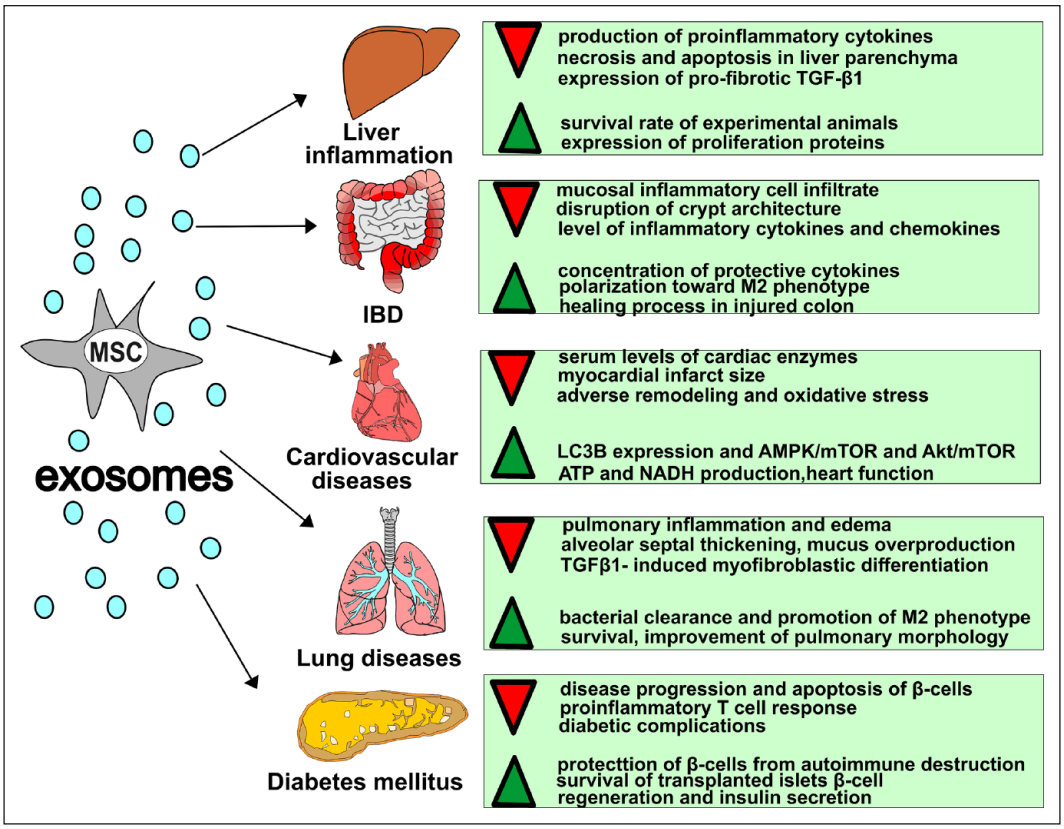

Figure 2. Therapeutic potential of MSC-Exo in immune-mediated diseases. MSC-Exo possess the capacity to decrease (▼) inflammation, apoptosis, fibrosis, and oxidative stress, while increase (▲) vasculogenesis and endogenous regeneration, making them an ideal candidate for the treatment of immune-mediated disorders. MSC: mesenchymal stem cell; IBD: inflammatory bowel disease; TGF-β1: transforming growth factor-beta 1; ATP: adenosine triphosphate; NADH: nicotinamide adenine dinucleotide + hydrogen; MSC-Exo: MSC-derived exosomes.

such as TNF-α, IL-6, IL-17, and IL-1β[36–38]. Liver tissue sections in MSC-Exo–treated hepatitis mice showed minimal infiltration of mononuclear cells with diminished necrosis and apoptosis in liver parenchyma[37,38]. In particular, the exosomal miR-223 inhibited the NLRP3 activation by binding to its 3′-UTR, leading to NLRP3 mRNA degradation and thus caspase-1–dependent inflammatory cell death, called pyroptosis was suppressed[38]. The activation of the apoptosis-related protein cleaved caspase-3 is another process that contributes to the mechanisms by which MSC-Exo inhibit liver apoptosis in experimental fulminant hepatic failure[37]. Tan and coworkers demonstrated that MSC-Exo protected hepatocytes from acetaminophen and hydrogen peroxide (H_2O_2)–induced apoptosis by decreasing caspase 3/7 level while upregulating anti-apoptotic gene Bcl-xL[39]. Although MSC-Exo do not regulate the anti-apoptotic effect through stress/defense-related genes that are commonly involved in the oxidative pathway namely heme oxygenase-1, glutathione peroxidase 4, glutathione reductase, and manganese superoxide dismutase[39], they offer antioxidant hepatoprotection against carbon tetrachloride (CCl_4) and H_2O_2 *in vivo*, in glutathione peroxidase 1 (Gpx1)-dependent manner[40]. Gpx1 reduces hepatic ROS and inhibits oxidative stress–induced apoptosis via upregulation of ERK1/2 and Bcl-2 and downregulation of the IKKB/NFkB/casp-9/-3 pathway[40].

The higher survival rate of experimental animals was also associated with upregulation of the priming-phase genes during liver regeneration, which subsequently led to higher expression of proliferation proteins (cyclin D1 and proliferation cell nuclear antigen) in the exosomes-treated group[39]. Moreover, Du and coworkers found that systemically injected human-induced pluripotent stem cell-MSC-Exo directly fused with hepatocytes, leading to increased expression of proliferation markers (proliferation cell nuclear antigen and phosphohistone-H3) in the livers of hepatic ischemia-reperfusion (I/R)-injured mice via activating sphingosine kinase and sphingosine-1-phosphate pathway in hepatocytes[41].

Liver fibrosis, which is the precursor to cirrhosis, is the result of the chronic inflammatory reactions and increased deposition of fibrillar collagens and other extracellular matrix proteins, primarily mediated by activated hepatic stellate cells (HSCs)[42]. The immunosuppressive effects of MSCs on continuous inflammation accompanying hepatic fibrosis are mainly attributed to MSC-derived secretomes. Accordingly,

Table 1. MSC-EV–Mediated Modulation of Macrophage Phenotype and Function.

MSC-derived extracellular vesicles	
Effects on macrophages	Disease model
Polarization of M1 into M2 macrophages	DSS-induced colitis
Upregulation of IL-10 and TGF-β production in macrophages	
Decreased level of macrophage-derived inflammatory cytokines and chemokines (TNF-α, IL-6, IL-1β, IL-7, CCL-17, and CCL-24)	
Reduced expression of iNOS	
Prevented generation of inflammatory phenotype in liver macrophages (Kupffer cells)	Acute liver inflammation
Suppressed production of inflammatory cytokines (TNF-α, IL-1β, and IL-6) in liver macrophages	
Reduced number of M1 macrophages and hepatic stellate cells	CCl_4-induced liver fibrosis
Modulate interaction of Kupffer cells and hepatic stellate cells in chronic liver inflammation	
Increased M2 macrophage marker expression	LPS-induced lung injury
Augmented phagocytic capacity	
Shifting the proportions of lung proinflammatory/classical and nonclassical monocytes and alveolar macrophages toward the anti-inflammatory profiles	Bleomycin-induced pulmonary fibrosis
Polarization of inflammatory macrophages to M2 phenotype	Peripheral neuropathy in diabetic mice
Decreased production of proinflammatory cytokines TNF-α and IL-1 in macrophages	
Promoting the M2 macrophage polarization through activating the PTEN/AKT signaling pathway	Diabetic wound

MSC-EV: mesenchymal stem cell-derived extracellular vesicles; IL: interleukin; CCL: C-C motif chemokine ligand; TGF-β: transforming growth factor-beta; DSS: dextran sodium sulfate; TNF: tumor necrosis factor; CCl_4: carbon tetrachloride; iNOS: inducible nitric oxide synthase; LPS: lipopolysaccharides; PTEN: phosphatase and tensin homolog protein; AKT: protein kinase B.

in CCl_4-stimulated chronic liver fibrosis, transplantation of exosomes derived from human umbilical cord MSC resulted with significant decrease in serum aspartate aminotransferase activity and expression of collagen type I and type III in the liver, associated with attenuated chronic hepatic inflammation and fibrosis[43]. MSC-EV prevented generation of inflammatory phenotype in liver macrophages (Kupffer cells) by inhibiting production of inflammatory mediators (TNF-α, IL-1β, and IL-6). Moreover, MSC-EV modulated expression of pro-fibrotic genes [collagen I, vimentin, alpha-smooth muscle actin (α-SMA), and fibronectin] in HSCs, the crucial players in the initiation, and progression of liver fibrosis[44]. Engineered miR-181-5p-overexpressing MSC-EVs increased expression of autophagy-related Beclin-1 and decreased expression of anti-apoptotic Bcl-2 in HSCs, resulting in their increased apoptotic cell death. Moreover, these modified MSC-EVs significantly reduced number of M1 macrophages and HSCs in the injured livers leading to the attenuation of chronic liver inflammation and fibrosis in mice[44] (Table 1).

Modulation of TGF-β signaling is one of the main mechanisms of MSC-based modulation of liver fibrosis. After binding to its receptor, TGF-β induces the activation of a signaling cascade leading to the proliferation of pro-fibrotic cells, myofibroblasts. The decreased expression of pro-fibrotic TGF-β1 and phosphorylation of Smad2 *in vivo*, accompanied with suppressed transcription of genes responsible for epithelial-to-mesenchymal transition (EMT) of hepatocyte, were noticed in the livers of animals that received MSC-Exo[43]. Moreover, MSC-Exo treatment reversed fibroblasts-like morphology, increased E-cadherin, and decreased N-cadherin and vimentin expression on human liver cells (HL7702) that underwent typical TGF-β1–induced EMT *in vitro*. These results indicated that the TGF-β1/Smad signaling pathway might be one of the prime targets for MSC-Exo–based anti-fibrotic therapies[43].

MSC-EV–Based Therapy of Inflammatory Bowel Diseases (IBDs)

Because of its potential to resolve colon inflammation and to enhance regeneration of damaged gut epithelium, MSC-derived secretome is considered as a promising therapeutic agent in the treatment of IBDs (Fig. 2)[44]. Activation of gut-infiltrated macrophages and dendritic cells (DCs) results with the induction of T cell–mediated immune response resulting with the progression of colon inflammation and development of IBD[45]. As recently evidenced by us and others, MSCs, in paracrine manner, attenuated experimental dextran sodium sulfate (DSS)-induced colitis in mice by enhancing production of anti-inflammatory cytokine IL-10 in colonic macrophages and promoting their polarization toward immunosuppressive M2 phenotype[46].

The fact that beneficial effects mediated by MSCs in colonic inflammation are mainly attributed to their secretory pathways rather than their tissue-homing capacity suggested that MSC-EV should be used in the treatment of IBD. Intraperitoneally administrated MSC-EV significantly alleviates acute DSS-induced colitis in mice according to survival rate, clinical symptoms, and colon length[47–50]. Moreover, histopathological analysis of colon tissue revealed

significant differences in histological score of colon injury among experimental groups. DSS + MSC-EV–treated mice exhibited reduced mucosal inflammatory cell infiltrate and only mild disruption of crypt architecture[47–50]. Several recently published studies demonstrated that MSC-EV alleviated murine colonic inflammation and maintained intestinal barrier integrity via a macrophage-dependent mechanism by inducing generation of immunosuppressive IL-10–producing M2 macrophages in the colon[47,50–53]. Accordingly, level of macrophage-derived inflammatory cytokines and chemokines that activate and maintain chronic T-cell–mediated mucosal inflammation in the gastrointestinal tract (TNF-α, IL-6, IL-1β, IL-7, C-C motif chemokine ligand (CCL)-17, and CCL-24) was decreased, while concentration of protective cytokines (IL-10 and TGF-β) was increased[47,50]. In line with results obtained *in vivo*, EVs derived from MSCs entered in lipopolysaccharides (LPS)-stimulated macrophages *in vitro* and induced their polarization toward M2 phenotype resulting in limited production of proinflammatory cytokines[47,50] (Table 1). Intravenous injection of MSC-EVs, containing microvesicles and exosomes, attenuated the severity of 2,4,6-trinitrobenzene sulfonic acid (TNBS)-induced colitis in rats by downregulating protein expression of inflammatory mediators such as TNF-α, IL-1β, cyclooxygenase-2, and iNOS and upregulating anti-inflammatory cytokine IL-10[51]. It was demonstrated that anti-inflammatory miR-146 carried by these vesicles had an anti-inflammatory effect in TNBS-induced colitis through the inhibition of nuclear factor kappa B p65 (NF-κB p65) signaling pathways[51], by targeting TNF receptor-associated factor 6 and IL-1 receptor-associated kinase 1[52]. This mechanism suppresses iNOS-driven signaling in colonic macrophages and attenuates colon injury[51,52]. Moreover, reduced NF-κB and mTOR activity and alleviated inflammation in the gastrointestinal tract could be due to MSC-EV–mediated downregulation of ubiquitin in mice with DSS-induced colitis[49]. MSC-EVs provided significant antioxidant defense in TNBS-treated animals, as demonstrated by increased superoxide dismutase and glutathione activity, leading to reduced generation of free radicals[51]. Yang and coworkers also demonstrated that MSC-EVs enhanced healing process in injured colon via attenuating colon apoptosis by inhibiting both the extrinsic death receptor signal pathway and the intrinsic mitochondrial signal pathway[51].

Therapeutic Efficacy of MSC-EV for Cardiovascular Diseases

Numerous studies have demonstrated that bioactive factors produced by MSCs provide improvement in a wide range of cardiac functions (decreased in scar tissue, reversed remodeling, increased blood vessel density, improved contractility, and increased left ventricular ejection fraction)[54–56], indicating their possible use in the therapy of cardiovascular pathology.

Administration of adipose tissue–derived MSC (AT-MSC) exosomes protected rat myocardium against I/R injury, as demonstrated by decreased serum levels of creatine kinase-myocardial band, lactate dehydrogenase, and cardiac troponin I[57]. MSC-Exo dramatically antagonized I/R-induced myocardial apoptosis by modulating the expression of major apoptosis-regulating genes (Bcl-2 and Bax) in infarcted myocardium through activation of Wnt/β-catenin signaling[57]. In addition, administration of MSC-Exo induced cardiomyocyte autophagy via upregulating myocardial LC3B expression and AMPK/mTOR and Akt/mTOR pathways, resulting in reduced myocardial infarct size and improved heart function in experimental animals (Fig. 2)[58]. Arslan and coworkers demonstrated that MSC-Exo not only reduced infarct size, but also resulted in a long-term preservation of cardiac function and reduced adverse remodeling[59]. The mode of action may be by increasing adenosine triphosphate (ATP) and nicotinamide adenine dinucleotide + hydrogen production, reducing oxidative stress, and activating PI3K/Akt pathway to enhance myocardial viability[59].

Several research groups highlighted *exosomal miRNAs* as *crucial* players in MSC-Exo–based attenuation of cardiac diseases. The possible mechanism for enhanced paracrine activity and cardioprotective effects of human endometrium-derived MSCs (EnMSCs) might involve elevated expression and cellular delivery of exosomal miR-21. EnMSC-Exo protected cardiomyocyte from apoptosis and increased microvessel density in ischemic hearts by reducing expression of phosphatase and tensin homolog protein (PTEN) and promoting protein kinase B (Akt)-dependent upregulation of Bcl-2 activity in injured cardiomyocyte[60]. Feng and coworkers showed that MSC-Exo–mediated delivery of miR-22 reduced apoptosis in ischemic cardiomyocytes, ameliorated fibrosis, and improved cardiac function in a mouse myocardial infarction model, by targeting methyl-CpG-binding protein 2, which was upregulated in ischemic hearts[61]. By using human engineered cardiac tissue technologies and mathematical simulations, Mayourian et al.[62] suggested that miR-21-5p plays an important role in MSC-Exo–mediated effects on cardiac contractility and calcium handling, likely via PI3K signaling. Exosomes secreted from GATA-4 overexpressing MSCs dramatically reduced myocardial I/R injury by delivering anti-apoptotic miR-19a into ischemic myocardium. miR-19a promoted *in vivo* cardiac function recovery by downregulating PTEN and BIM, proposed mediators controlling cardiomyocytes survival through the activation of Akt and ERK signaling pathways[63].

MSC-Derived Secretome in the Treatment of Lung Diseases

Therapeutic potential of MSC-EV in inflammatory lung diseases such as acute respiratory distress syndrome, asthma, chronic obstructive pulmonary diseases (COPD), and idiopathic pulmonary fibrosis (IPF) is based on their capacity to

modulate immune response, suppress apoptosis, attenuate fibrosis, and promote regeneration of injured respiratory epithelium.

Several research groups demonstrated that enhanced bacterial clearance and reduced pulmonary inflammation and edema were essential for the therapeutic effects of human MSC-EV in endotoxin-induced acute lung injury in mice[64–66]. Initially, after the uptake of MSC-EV by alveolar type 2 cells in CD44 receptor-dependent manner, microvesicles increase intracellular ATP levels by upregulating α1 subunit of Na^+-K^+-ATPase in lung epithelium. Morrison and coworkers demonstrated that administration of human BM-derived MSC-EV ameliorates lung injury in LPS-injured mice by promoting an anti-inflammatory and highly phagocytic macrophage phenotype (M2)[67]. Moreover, MSC-derived keratinocyte growth factor decreased influx of neutrophils, enhanced monocyte phagocytosis of bacteria, and reduced vascular permeability, leading to improved survival of experimental animals[64–66].

COPD is characterized by persistent limitation of expiratory airflow, defects in tissue repair, chronic inflammation of the airways, and abnormal lung inflammatory response to toxic particles or gases (eg, cigarette smoke)[68]. Recent advances in the regenerative medicine suggest that MSC-EVs possess a therapeutic potential which is similar to the stem cells of their origin and may be used as a new cell-free–based therapy for the treatment of COPD[69]. Maremanda et al.[70] reported that exosomes from mouse MSCs could relieve cigarette smoke–induced inflammation and mitochondrial dysfunction in mice and human lung epithelial cells. Human umbilical cord derived–MSC-EV significantly alleviated peribronchial and perivascular inflammation, reduced alveolar septal thickening, and decreased mucus overproduction[69]. Microarray analysis revealed that MSC-EV modulates signaling pathways known to be associated with COPD, in particular reduced production of zeta C kinase and levels of NF-κB subunit p65 in the cigarette smoke–exposed lung[69]. Having in mind that FGF2 is important in lung development and has regenerative capacity, Kim and colleagues designed FGF2-bearing MSC-derived artificial nanovesicles and suggested that the regenerative effect of these vesicles is mediated by the stimulation of recipient growth factor signaling via fibroblast growth factor-2 (FGF2)[71].

Since MSC-derived secretome may suppress production of degrading enzymes, and inhibit secretion of profibrotic factors in lung-infiltrated immune cells, several experimental studies investigated therapeutic effects of MSC-EV in the treatment of IPF. Shentu and coworkers indicated that MSC-EVs exert anti-fibrotic effects relevant to pulmonary fibrosis, dependent on surface expression of Thy-1 and interaction of Thy-1 with beta integrins mediates MSC-EV uptake by lung fibroblasts[72,73]. miR-630-enriched MSC-EVs block TGFβ1-induced myofibroblastic differentiation and consequently attenuate IPF[72]. Single intravenous dose of purified exosomes derived from human BM MSCs effectively prevented and attenuated core features of bleomycin-induced pulmonary fibrosis in mice, improving pulmonary morphology, blunting collagen deposition, and restoring lung architecture[74]. MSC-EV modulated lung macrophage phenotypes, shifting the proportions of lung proinflammatory/classical and nonclassical monocytes and alveolar macrophages toward the monocyte/macrophage profiles of control mice (Fig. 2, Table 1)[74]. Administration of MSC-EV significantly downregulated α-SMA expression and improved histopathological fibrosis, indicating therapeutic effects of these vesicles through modification of the myofibroblastic phenotype in IPF[73].

In the mouse model of ovalbumin-induced allergic asthma, Exo obtained from human AT-MSCs effectively reduced eosinophil counts in lung tissue and bronchoalveolar lavage fluid[75]. Collagen fiber deposition as well as expression of profibrotic TGF-β in airways and asthmatic lung tissue were downregulated in MSC-EV–treated animals leading to reduced airway remodeling[75]. Similarly, in neutrophilic-mediated allergic airway inflammation, induced by repeated mucosal exposure to *Aspergillus hyphal* extract (AHE) in immunocompetent mice, systemic administration of MSC-EV significantly ameliorated the AHE-provoked increases in airway hyperreactivity, lung inflammation, and the antigen-specific CD4 T-cell Th2 and Th17 phenotype[76]. Du et al.[77] isolated exosomes secreted by MSCs and investigated their immunomodulation effect on peripheral blood mononuclear cells (PBMCs) of asthmatic patient. These authors revealed that MSC-Exo upregulate IL-10 and TGF-β1 from PBMCs, thus promoting the proliferation and immunosuppressive ability of regulatory T cells[77].

MSC-EV in the Treatment of Diabetes Mellitus (DM) and Its Complications

The use of MSC-Exo may be a promising treatment strategy for DM and its complications, because MSC-Exo contain a rich array of growth cytokines, repair proteins, and therapeutic noncoding RNAs, which regulate inflammation, vascularization, and anti-apoptotic mechanisms, and thus promote the repair of organs damaged by prolonged hyperglycemia[78].

MSC-Exo protect β-cells from autoimmune destruction, impede the disease progression, and enhance the survival of transplanted islets (Fig. 2)[79]. It has been reported that menstrual blood–derived MSC-Exo enhance β-cell regeneration and insulin secretion in rat models of T1DM through pancreatic and duodenal homeobox 1 pathway[80]. MSC-EVs possess immunomodulatory effects, by inhibiting proinflammatory T cell response against the glutamic acid decarboxylase (GAD) antigen and inducing regulatory phenotype of DCs[81]. The results of *in vivo* experiments suggest that AT-MSC-Exo ameliorate the autoimmune response in mice

with streptozotocin (STZ)-induced T1DM, as they increase the population of regulatory T cells and their cytokines, without affecting the proliferation index of lymphocytes[82].

Moreover, exosomes from human umbilical cord MSC (hucMSC-Exo) possess the ability to reverse peripheral insulin resistance and alleviate apoptosis of β-cells induced by STZ-induced type 2 DM in rats[83]. Specifically, hucMSC-Exo restored phosphorylation at the tyrosine site of insulin receptor substrate 1 and protein kinase B in T2DM stimulated the expression and translocation of glucose transporter 4 to the muscle cell membrane and enhanced the storage of glycogen in the liver, thereby promoting the maintenance of glucose homeostasis[83].

MSC-Exo are also emerging as potential therapeutic weapon in the treatment of diabetic complications[78]. The administration of MSC-EV rich in therapeutic noncoding RNAs may offer a novel approach to the prevention and treatment of diabetic retinopathy (DR). Zhang and coworkers have shown that MSC-Exo with overexpressed *miR-126* induced a significant downregulation of HMGB1, NLRP3, and NF-κB/p65 protein expression in DR rats, thereby inhibiting the production of different inflammatory cytokines and attenuating retinal vascular endothelial damage[84]. It was demonstrated that *miR-221*/*miR-222* family can modulate angiogenesis via the c-Kit receptor[85]. Adipose MSC-Exo could transfer *miR-222* to retinal cells and control the expression of STAT5 protein, thereby inhibiting neovascularization in DR and promoting retinal regeneration in rabbit[86].

Diabetic nephropathy (DN). DN is a serious microvascular diabetic complication that eventually develops into end-stage renal disease[87]. MSC-Exo demonstrate a substantial protective impact on both acute and chronic kidney injury and are rich in growth factors such as epidermal growth factor (EGF), FGF, HGF, and VEGF and contain therapeutic noncoding RNAs such as miR-215-5p, miR-486, miR-150, miR-134, and miR-16-5p which improve renal function, delay renal fibrosis, and repair podocyte function[78]. It has been shown that TGF-β1 has a significant role in renal fibrosis and through the inhibition of TGF-β1 secretion, MSC-Exo reduce the epithelial–endothelial mesenchymal transition and prevent mesangial cell proliferation mediated by MAPKs and PI3K/AKT/mTOR pathways, leading to the attenuation of renal fibrosis[88]. Jiang et al.[89] demonstrated that exosomes released by human urine–derived stem cells possess the ability to prevent podocyte apoptosis and stimulate cell survival as well as vascular regeneration in T1DM rats. Another study demonstrated that MSC-derived exosomal miR-let7c attenuated kidney damage by preventing renal fibrosis in C57BL/6J mice, which are susceptible to comorbidities such as diet-induced obesity and type 2 diabetes[90].

Diabetic polyneuropathy (DPN) is a chronic microvascular complication of diabetes, which involves inflammation as a crucial element, with the inflammatory response and cytokines being pivotal factors in this process[91]. Administration of rat BM-MSC-EV was followed by therapeutic benefit in improving cognitive function in STZ-induced diabetic mice by repairing damaged neurons and astrocytes[92]. Fan and coworkers demonstrated that MSC-EV treatment ameliorated peripheral neuropathy in diabetic mice by stimulating the polarization of inflammatory macrophages to M2 phenotype and decreasing the levels of proinflammatory cytokines TNF-α and IL-1, increasing the axonal myelination and improving the vascular dysfunction in peripheral nerve tissues[93] (Table 1). Bioinformatics analysis showed that MSC-EV are enriched with abundant miRNAs including let-7a, miR-23a, and miR-125b, among others, that synergistically targeted and downregulated the Toll-like receptor 4/NF-κB and receptor for advanced glycation end product signaling pathway which is well-known in the pathogenesis of DPN[93–95].

Diabetic cardiomyopathy is a complication defined as ventricular dysfunction in the absence of hypertension, coronary artery, and valvular heart disease, which eventually develops into heart failure and MSC-EVs are promising therapeutic tools in its treatment. Lin et al. performed a study where MSC-EVs were administered in a rat model of diabetic myocardial injury. The results showed that after the treatment with MSC-derived EV, there was a significant reduction observed in the level of left ventricular collagen and that MSC-Exo inhibited the TGF-β1/Smad2 signaling pathway, which lead to the attenuation of myocardial injury and fibrosis[96].

Diabetic wounds often occur in diabetic patients and MSC-Exo have demonstrated benefit in the treatment of diabetic wound healing by promoting the M2 macrophage polarization through activating the PTEN/AKT signaling pathway[97] (Table 1). In addition, MSC-EVs are rich in growth factors such as VEGF, IL-8, HGF, and human T-cell factor 4, which have pro-angiogenic activity and can stimulate the vascularization of the wounds[98].

Erectile dysfunction is a common chronic diabetic complication and injection therapy with AT-MSC-Exo can promote the recovery of erectile function in DM rats by increasing the ratio of intracavernosal pressure to mean arterial pressure and upregulating the expression of atrial natriuretic peptide, brain natriuretic peptide, and neuronal nitric oxide synthase[99].

Tracking and Biodistribution of MSC-EVs

Although MSC-EVs are considered as a promising "cell-free" therapeutic, much remains unknown about the *in vivo* properties and the fate of injected vesicles. Tissue distribution and pharmacokinetics of MSC-EV upon administration are crucial parameters that will define their biological role and therapeutic effectiveness. Successful implementation of MSC-EV therapies for immune-mediated diseases requires a better understanding of their fate after transplantation, thus

huge efforts are being made to improve labeling and tracking methods. The vast majority of animal studies of MSC-EV therapeutic effects have used systemic routes of administrations. Labeling of nano-sized vesicles with fluorescent dyes and visualization with *in vivo* optical imaging demonstrated that biodistribution of systemically administered MSC-EV is a dynamic process. After accumulation in the liver, spleen, and lungs within approximately 30 min upon administration, exosomes are eliminated via hepatic and renal processing within a few hours[100]. Although the efficacy of fluorescently labeled MSC-EV for tracking has been shown in several preclinical studies[101–104], the main limitation of this direct labeling is "dilution" of the marker after exosome administration. In particular, significant amount of fluorescent dye dissociated from nanovesicles, and can spontaneously form Exo-like particles, thus radiolabeling of MSC-EV is an alternative tracking method[105]. Among all the magnetic particles, labeling of Exo with superparamagnetic iron-oxide is the most widely used and developed method, providing high resolution and sensitive magnetic resonance imaging and precise detection of particles in deep organs[106].

In vivo tracking studies clearly demonstrated that exosomes are capable to home to the site of pathophysiological process, when active inflammation is present[107]. In particular, as a consequence of increased permeability and blood–brain barrier (BBB) damage, injected exosomes from the blood are able to migrate across the BBB, modulating an inflammatory response and leading to various regenerative effects[108–111]. Near-infrared (NIR) dyes are ideal for *in vivo* applications due to their high signal/noise ratio. Grange and coworkers showed that NIR dye-labeled EVs derived from human MSCs accelerated recovery following acute kidney injury *in vivo*, by accumulating specifically in the kidneys of mice[103]. DiD is a lipophilic membrane dye having emission in the far-red region of the spectrum. This dye is used for *in vivo* imaging, as most tissues do not autofluorescence in this range and these wavelengths have less phototoxicity[103]. DiD-labeled MSC-EVs accumulated in liver and spleen and, to a lesser extent, in BM, femur, and tibia, and were not found in the lungs, heart, and kidneys in radiation-induced damage in mice[112]. Mendt et al.[101] provide a report on the production process and the potential of MSCs in the generation and engineering of iExosomes for human trials and tested the efficacy of GMP-grade MSC-derived iExosomes in several assays and mouse models of pancreatic cancer. To test biodistribution of EVs, they used 1,1′-dioctadecyltetramethyl indotricarbocyanine iodide in their experiments. Intravenously injected labeled MSC-EVs accumulated mainly in the pancreas of tumor-bearing mice after 3, 6, 24, and 48 h. The signal was lower in the liver, spleen, and lungs, and other internal organs. Importantly, the preferential accumulation of MSC-EVs in tumor when vesicles were injected intravenously in mice bearing tumors was observed[101]. Having in mind that the distribution profile of MSC-EV depends on the route of administration and accompanying injuries and diseases, the nebulized route constitutes a particularly interesting route of administration in the context of lung damage. Nebulized MSC-EVs exerted protective effects in severe pneumonia caused by *Pseudomonas aeruginosa* in mice, and nebulized clinical-grade human adipose-derived MSC-EVs were safe in healthy volunteers without serious side effects. Biodistribution of MSC-EV labeled with the fluorescent cell membrane dye DiR (1,1-dioctadecyl-3,3,3,3-tetramethylindotricarbocyanine iodide) *in vivo* showed that the lung's fluorescence intensity peaked at 24 h post nebulization and then gradually decreased up to 28 days in mice. Interestingly, the intensity remained to be detected within the stomach at 24 h. A systemic diffusion of labeled EVs might be explained by the possibility of EVs swallowing during the nebulization process, similar to a kind of "oral route"[113]. A new labeling and tracking technique of MSC-EV with Cre-recombinase in loxP reporter animals has been used; however, these engineering methods might change the phenotype and functions of the derived exosomes[107]. Thus, it could be concluded that the ideal method of MSC-EV labeling for efficient tracking after transplantation remains a challenging issue that requires further investigation.

Conclusion and Future Directions

EV-based therapy is considered to be a new hope in transplantation medicine. With the recent burst of research, MSC-EVs are now widely accepted as next-generation cell-free therapeutics for intractable disease, since they convey most of the therapeutic properties of MSCs. Results from broad range of experimental studies indicate that MSC-Exo are the promising therapeutic for the therapy of immune-mediated diseases; however, there is still a lot of research work to be done before their clinical applications. It was demonstrated that MSC-EVs affect maturation and function of immune cells and modulate both innate and adaptive immunity. However, although the immunomodulatory effects of MSC-EV are well described, future preclinical and clinical studies should explore the mechanisms that regulate the timely expression of these products which will enable their appropriate clinical use. Having in mind that present laboratory protocols are based on unstandardized data regarding the exosome diameter and membrane markers, novel studies should define exact parameters for particles' isolation in the aim to obtain the purity of the therapeutic before its medical use. Moreover, it is important to define protocols for quality control of derived MSC-EV to entirely exploit their therapeutic capacity. For wide use of MSC-EV in regenerative medicine, there are also unresolved issues regarding the large-scale manufacturing of MSC-EV and their long-term storage. In addition, appropriate dose, administration method, and time of the application must be precisely formulated in the aim to manage the right balance between safeness and effectiveness of MSC-Exo–based therapy. Thus, efforts directed toward determining standards on the therapy

efficacy and safety issues will speed up clinical implementation of MSC-Exo as regenerative agents. New techniques may help in filling the gap of knowledge regarding biodistribution, pharmacokinetics, and possibility of targeted delivery of MSC-EV and to further promote clinical translation of MSC-EV–based regenerative therapy.

Author Contributions

Z.I.: manuscript writing, collection of data; B.LJ.: manuscript writing, collection of data; D.P.: manuscript writing, creation of figures; V.M.: manuscript writing; M.G.J: conception and design, manuscript writing, collection of data, interpretation of data.

Ethical Approval

Not applicable.

Statement of Human and Animal Rights

This article does not contain any studies with human or animal subjects.

Statement of Informed Consent

Not applicable.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This study was supported by the Ministry of Education, Science and Technological Development of the Republic of Serbia (Agreement No. 175103, Agreement No. 451-03-68/2020-14/200107, Agreement No. 451-03-9/2021-14/200378, Agreement No. 451-03-47/2023-01/200111) and by Faculty of Medical Sciences, University of Kragujevac, Serbia (JP 05/20).

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