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OPINION REVIEW

Mesenchymal stem cells from different sources and their derived exosomes: A pre-clinical perspective

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Abstract

Since the introduction of cell therapy as a strategy for the treatment of many diseases, mesenchymal stem cells have emerged as ideal candidates, yet the underlying mechanisms of their beneficial effects are only partially understood. At the start of the 21st century, a paracrine effect was proposed as a mechanism of tissue repair by these cells. In addition, a role was suggested for a heterogeneous population of extracellular vesicles in cell-to-cell communication. Some of these vesicles including exosomes have been isolated from most fluids and cells, as well as from supernatants of *in vitro* cell cultures. Recent research in the field of regenerative medicine suggests that exosomes derived from mesenchymal stem cells could be a powerful new therapeutic tool. This review examines the therapeutic potential of these exosomes obtained from the sources most used in cell therapy: bone marrow, adipose tissue, and umbilical cord.

Key words: Mesenchymal stem cells; Exosomes; Cellular therapy

Core tip: This article reviews the use of exosomes derived from mesenchymal stem cells to treat various disease states and discusses their possible clinical applications.

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INTRODUCTION

At the start of the 21st century, cell therapy, defined as a series of strategies based on the use of living cells for therapeutic purposes, emerged as a promising tool in the field of biomedicine. The aim of cell therapy is to repair, replace or restore the biological functions of an organ or of damaged tissue. Research efforts in regenerative medicine have mainly focused on the use of mesenchymal stem cells (MSC).

Friedenstein and co-workers were the first to discover MSC. These authors showed that bone marrow (BM) contains a population of cells with a high proliferative capacity that adheres to plastic in culture[1]. Since this observation in the 1970s, many studies have focused on this type of adult stem cell. However, there was no defined approach to characterize MSC and different methods of isolation, expansion and characterization were reported. This made it difficult to compare findings between independent laboratories. To resolve this issue, in 2006, the Mesenchymal and Tissue Stem Cell Committee of the International Society for Cellular Therapy proposed minimal criteria to define human MSC: They should be plastic-adherent when maintained in standard culture conditions; they must express specific surface antigens; and they should also show multipotent cell differentiation potential *in vitro*[2]. These criteria facilitated the work of many groups which continued their research with this cell type. MSC have been successfully obtained from many sources including adipose tissue, Wharton's Jelly, placenta, dental pulp or amniotic fluid among others[3]. Furthermore, throughout the years, the regenerative capacity of MSC and their immunoregulatory properties have been well documented[4].

Due to their characteristics, MSC offer great therapeutic potential and many therapies based on these cells have been developed to treat a wide range of disorders. However, despite good results, the underlying mechanisms of their beneficial impacts are only partially understood. One hypothesis is that MSC induce tissue regeneration through their capacity to migrate to the site of injury and then to differentiate into the corresponding cells in the damaged tissue. In 2005, Gnecchi *et al*[5] were among the first to propose a paracrine effect of MSC in tissue regeneration[5]. Since then, many studies have shown these effects of MSC[6,7] and it is recognized today that, besides releasing cytokines and growth factors, MSC also secrete extracellular vesicles (EV), which are thought to play an important role in tissue regeneration and immunomodulation[4]. Based on these data, recent research has focused on EV derived from MSC as a form of non-cellular therapy[8].

The term EV refers to a heterogeneous population of vesicles[9]. For several decades, the presence of membrane-enclosed vesicles outside solid tissue cells, as well as biological fluids such as blood or semen, was described[10]. These vesicles were considered a vehicle for the cell to discard unwanted proteins[11]. In the first decade of the 21st century, two independent research groups demonstrated the presence of RNA, including miRNA in EV. This finding has rekindled interest in EV as possible mediators of cell-to-cell communication[12,13]. The International Society for Extracellular Vesicles proposed minimum criteria for their definition: EV is the generic term for particles naturally released from the cell that are delimited by a lipid bilayer and cannot replicate, *i.e.* they do not contain a functional nucleus[14]. To date, EV have been isolated from most fluids and cells[15] and from supernatants of *in vitro* cell cultures[16]. It has also been established that the release of EV is an evolutionarily well-conserved mechanism that the cells exploit for the exchange of bioactive proteins, lipids and nucleic acids[17].

The term EV encompasses microvesicles/nanoparticles/vesicles, apoptotic bodies and exosomes[16]. Exosomes are small EV generated thought inward budding of endosomal membranes. While the definition of exosomes is not completely clear, they are negatively charged lipid-bilayer vesicles of diameter 30-100 nm and density 1.13-1.19 g/mL. Exosomes are secreted by fusion of the multivesicular body containing exosomes with the plasma membrane[18]. The protein content of exosomes has been extensively studied since their initial description. So far, it is known that the composition of exosomal proteins varies among cell types. However, proteins such as Alix, Tsg101 and tetraspanins including CD9, CD63 or CD81 are frequent components and are often used as exosome markers[19].

Several studies have suggested that exosomes derived from MSC could serve as a novel therapeutic tool in the field of regenerative medicine. The main benefit proposed is that as no cells are introduced, mutated or damaged genetic material that could negatively affect the recipient is avoided. Another advantage is that exosomes lack immunogenicity[20]. As a shortcoming, exosomes are static and do not reproduce *in vivo*[21].

While MSC can be found in most adult tissues, the major sources of MSC for therapeutic use have been bone marrow, adipose tissue and umbilical cord[22]. This review updates research addressing the therapeutic potential of exosomes derived

from MSC obtained from these tissues.

EXOSOMES DERIVED FROM BONE MARROW MSC

MSC derived from bone marrow are probably the most commonly used stem cells in clinical trials. The use of bone marrow MSC derived exosomes (BM MSC-Ex) as a promising tool for future therapies has been examined in experimental models of various pathologies. In a model of liver disease, Damania *et al*[23] employed rat BM MSC conditioned medium in *in vitro* and *in vivo* experiments. The rich exosome fraction obtained through ultracentrifugation of this medium was found to have antiapoptotic and antioxidant effects in *in vitro* models of liver injury and to improve liver regeneration and recovery from liver injury *in vivo*. These results are in accordance with those reported by Rong *et al*[24] who, using a rat model of liver fibrosis, observed that the administration of BM MSC-Ex improved this fibrosis. Furthermore, these authors proposed that the beneficial effects of these exosomes consisted of inhibition of the Wnt/β-catenin signaling pathway and suggested their use to treat liver disease in a clinical setting[24]. The therapeutic potential of BM MSC-Ex in degenerative diseases, such as intervertebral disc degeneration (IDD), has been advocated by several researchers. IDD is a cause of lower back pain related to degenerative musculoskeletal disorders affecting large numbers of patients. Liao *et al*[25], using human BM MSC-Ex in a rat tail model proposed that exosomes may delay or prevent disc degeneration. Exosomes could modulate endoplasmic reticulum stress and protect against nucleus pulposus cell death. The therapeutic effects of BM MSC-Ex on IDD are supported by the findings of another study conducted in an IDD model in rabbits. In this work, Xia *et al*[26] proposed that the use of BM MSC-Ex significantly prevents the progression of degeneration *via* anti-oxidant and anti-inflammatory effects. The use of BM MSC-Ex for the treatment of cancer has also been explored by several groups. Recently, BM MSC-Ex overexpressing (exogenous) miR-34a, a recognized tumor suppressor, were reported to ameliorate glioblastoma in a mouse model[27]. In another experimental study on pancreatic cancer, Wu *et al*[28] observed that BM MSC-Ex-derived miRNA-126-3p blocked the progression of this cancer.

Zhu *et al*[29] found that exosomes derived from different cell types had different therapeutic effects. This hypothesis is consistent with recently published data by the same group. When comparing the effects of exosomes obtained from healthy or diabetic rats in a rat calvarial defect, these authors observed a more positive effect when exosomes from rats without type-1 diabetes were used. Accordingly, they proposed that for patients with type-1 diabetes, the autologous transplantation of BM MSC-Ex to promote regeneration could be inappropriate[30].

According to the literature, the potential of BM MSC-Ex for the treatment of various pathologies seems evident. However, in terms of clinical applications we have only found a letter to the Editor in which their use to treat graft *vs* host disease (GvHD) is described. BM-MSC have been employed in the treatment of GvHD in clinical practice since Blanc *et al*[31] published their encouraging results for the treatment of refractory GvHD. In one patient, Kordelas *et al*[32] used an exosome-enriched fraction processed from collected MSC supernatants instead of administering the MSC themselves. The patient was stable for several months post-exosome application. Although the patient died of pneumonia 7 months after treatment, the authors concluded that BM MSC-Ex could be a new safe tool to treat therapy-refractory GvHD and most likely other inflammation-associated diseases[32]. The improvement observed in this patient is supported by work conducted in mouse models[33,34].

EXOSOMES DERIVED FROM ADIPOSE MSC

As with BM MSC-Ex, there are many literature descriptions of the use of exosomes derived from adipose MSC (AMSC-Ex), in which a paracrine effect is produced both *in vivo* and *in vitro*. Several research groups have reported positive effects of AMSC-Ex in various skin disorders. Cho *et al*[35] were the first to investigate the therapeutic effect of AMSC-Ex in an atopic dermatitis mouse model. Taken together, the results suggested that AMSC-Ex could be a novel cell-free treatment for atopic dermatitis. The limitations reported by these authors were that AMSC donor age seemed to affect their immunomodulatory properties. Accordingly, they proposed to continue working on this issue to determine whether the potential of AMSC-Ex could be influenced by age[35]. Treatment of cutaneous wound healing has also been explored using exosomes derived from AMSC. To improve the retention of exosomes in the target area, Liu *et al*[36] proposed the use of hyaluronic acid and examined the effect of

AMSC-Ex combined with hyaluronic acid for acute cutaneous wound healing in nude mice. These authors concluded that this preparation of exosomes combined with appropriate scaffolds was effective. Their results showed that AMSC-Ex could markedly promote fibroblast activities, re-epithelialization and vascularization in wound healing[36]. Other studies have shown that AMSC-Ex accelerate wound healing *via* optimizing fibroblast function and collagen deposition[37]. Furthermore, Shen *et al*[38] detected a role for AMSC-Ex in corneal stromal cell and extracellular matrix remodeling.

Other disease states such as heart and neural conditions or cancer have also been examined as targets of AMSC-Ex therapy. The results of *in vitro* experiments by Liu *et al*[39] indicated that apoptosis induced by oxidative stress in the cardiomyocyte was blocked by AMSC-Ex. Others have reported the inhibition of ovarian cancer cell proliferation by exosomes collected from AMSC conditioned medium[40]. Feng *et al*[41] also argued that the use of AMSC-Ex to inhibit the activation of microglia cells and prevent neuroinflammation could be a promising therapeutic strategy for nerve injury.

EXOSOMES DERIVED FROM UMBILICAL CORD MSC

Umbilical cord MSC and their exosomes have also been examined as potential therapeutic tools in regenerative medicine. However, as for exosomes derived from other sources, the underlying mechanisms are still not well understood. Zhang *et al*[42] suggested that exosomes derived from umbilical cord MSC (UcMSC-Ex) enhanced angiogenesis through the Wnt4/β-catenin pathway, which could be an important mechanism responsible for cutaneous wound healing. This positive effect on angiogenesis has also been reported by another group. Hence, the authors of a recent study reported that transplantation of UcMSC-Ex markedly enhanced angiogenesis and bone healing in a rat model of femoral fracture. Their results unveiled a novel role of exosomes in accelerating fracture healing *via* the promotion of angiogenesis[43]. The results of both these studies are in accordance with the data reported by Zhou *et al*[44]. These last authors explored the impacts of human UcMSC-Ex on fracture healing by acting on the Wnt signaling pathway. They concluded that UcMSC-Ex could participate in repairing fractures in rats through this pathway.

Mao *et al*[45] investigated the effects of UcMSC-Ex in a model of induced inflammatory bowel disease. According to their findings, UcMSC-Ex are able to substantially alleviate induced inflammatory bowel disease in mice and may exert their impact through IL-7 expression modulation in macrophages. Other authors have assessed the immunosuppression and therapeutic effects of UcMSC-Ex used to treat colitis in a mouse model. Exosomes were obtained from MSC cultures in defined medium thus avoiding the use of fetal bovine serum. The results indicated that UcMSC-Ex alleviate colon damage in an animal disease model and have immunosuppressive effects *in vitro*[46]. These results have interesting implications for the clinical use of this type of therapy. Due to their immunosuppressive activity, autoimmune diseases have been a popular target of MSC therapy. This activity has been related to the secretion of soluble factors. Bai *et al*[47] analyzed the effect of UcMSC-Ex in an experimental model of autoimmune uveitis. The results revealed the therapeutic potential of exosomes for this condition. Bearing in mind that this is a major cause of visual impairment worldwide, these are promising results. Zhang *et al*[48] in 2018 addressed the clinical treatment of another common cause of visual impairment, idiopathic macular hole. This work is interesting because, as previously mentioned, the translation of exosome-based therapies to clinical practice is still very limited. Five patients with large, long-standing idiopathic macular holes were treated with an intravitreal UcMSC-Ex injection. The authors proposed that these exosomes could improve anatomic and visual outcomes of surgery for that disease, and suggested the need for a clinical trial with a greater number of patients[48]. In a mouse model of acute liver failure, Jiang *et al*[49] observed that UcMSC-Ex decreased the expression of the NLRP3 inflammasome and improved acute liver failure in that model. Animal models have also been used to examine the treatment of ischemic heart disease using exosomes. In a recent study, Han *et al*[50] encapsulated UcMSC-Ex in a functional peptide hydrogel designed to increase the retention and stability of exosomes. The hydrogel containing UcMSC-Ex was then used in a rat myocardial infarction model, injecting it into the infarcted border of the heart. The authors concluded that this is an effective way of harnessing exosomes for cardiac regeneration[50].

The data available in the literature related to the use of exosomes derived from different MSC to treat various pathologies are practically all at the experimental stage.

These data supporting their therapeutic potential are summarized in Table 1, Table 2 and Table 3. Although many studies have interesting clinical implications, there are still few data on the clinical use of exosomes including very few registered trials (www.ClinicalTrials.gov).

There is still much work to do. The optimization and standardization of obtaining exosomes is an important goal. Some authors advocate inducing hypoxia or stress in exosome-producing cells to increase exosome production[18]. This could be an interesting way of generating exosomes for clinical applications. Another interesting issue is related to adjusting doses for treatment. Further questions that need to be addressed are: Which is the ideal time to administer exosomes? Will scaffolds be necessary in some applications? The different laboratories are presently working on these issues to standardize how exosomes are obtained.

CONCLUSION

In summary, cell therapy "without cells", is an emerging field. While still at the experimental level, recent research efforts are starting to explore its translation to clinical practice. In the meantime, research into MSC cell therapy continues and there are hundreds of registered trials at different stages. We envisage that clinical trials in the near future will compare the benefits and shortcomings of cell therapy with and without cells.

Table 1 Exosomes derived from bone marrow mesenchymal stem cells

	In vitro study	*In vivo* study (animal model / clinical use)	Results	Ref.
Liver disease	+	Liver injury model (Rat)	Improves liver regeneration and recovery	Damania *et al*[23], 2018
Liver disease	+	Liver fibrosis model (Rat)	Reduces liver fibrosis	Rong *et al*[24], 2019
Intervertebral disc degeneration	-	Tail model (Rat)	Prevents disc degeneration progression	Liao *et al*[25], 2019
Intervertebral disc degeneration	+	IDD model (Rabbit)	Prevents the progression of degeneration *via* anti-oxidant and anti-inflammatory effects	Xia *et al*[26], 2019
Cancer	+	Xenografted with glioblastoma cells (Nude mice)	Improves glioblastoma	Wang *et al*[27], 2019
Cancer	+	Pancreatic cancer cells xenografted (Nude mice)	Inhibits cancer development	Wu *et al*[28], 2019
Bone regeneration	+	Calvarian defect (Rat)	Promotes bone regeneration and neovascularization	Zhu *et al*[30], 2019
Graft *vs* host disease	+	GvHD model (Mouse)	Enhances Treg production *in vitro* and *in vivo*	Zhang *et al*[34], 2018
Graft *vs* host disease	+	GvHD model (Mouse)	Ameliorates aGvHD *via* the therapeutic infusion of BM MSC-Ex	Fuji *et al*[33], 2018
Graft *vs* host disease	-	Clinical patient	Patient stable for several months after exosome application	Kordelas *et al*[32], 2014

GvHD: Graft *vs* host disease; BM MSC-Ex: Bone marrow mesenchymal stem cells derived exosomes; IDD: Intervertebral disc degeneration.

Table 2 Exosomes derived from adipose mesenchymal stem cells

Condition	*In vitro* study	*In vivo* study (animal model / clinical use)	Results	Ref.
Atopic dermatitis	-	Atopic dermatitis model (Mouse)	Reduces clinical symptoms	Cho *et al*[35], 2018
Acute cutaneous wound healing	-	Acute cutaneous wound healing (Nude mice)	Promotes fibroblast activities, re-epithelialization, vascularization in wound healing	Liu *et al*[36], 2019
Wound healing	+	Mouse full-thickness incision wound model	Accelerates wound healing by optimizing fibroblast function	Zhang *et al*[37], 2018
Corneal stromal cells	+	-	Role of ASC-Ex in corneal stromal cell and extra cellular matrix remodeling	Shen *et al*[38], 2018
Apoptosis in cardiomyocyte caused by oxidative stress	+	-	Prevents apoptosis	Liu *et al*[39], 2019
Ovarian cancer	+	-	Ovarian cancer cells inhibited by exosomes	Reza *et al*[40], 2016
Neural injury	+	-	Could inhibit the activation of microglia cells and prevent neuroinflammation	Feng *et al*[41], 2019

ASC-Ex: Exosomes derived from adipose mesenchymal stem cells.

Table 3 Exosomes derived from umbilical cord mesenchymal stem cells

Condition	*In vitro* study	*In vivo* study (animal model / clinical use)	Results	Ref.
Cutaneous wound healing	+	Wound model (Rat)	Proangiogenic effect	Zhang *et al*[42], 2015
Bone healing	+	Femoral fracture model (Rat)	Accelerated fracture healing *via* the promotion of angiogenesis	Zhang *et al*[43], 2019
Bone healing	-	Fracture model (Rat)	Repairs fractures in rats through the Wnt signaling pathway	Zhou *et al*[44], 2019
Inflammatory bowel disease	+	Inflammatory bowel disease model (Mouse)	Alleviates induced inflammatory bowel disease	Mao *et al*[45], 2017
Acute liver failure	+	Liver injury model (Mouse)	Decreases acute liver failure in that model	Jiang *et al*[49], 2019
Colitis	+	Colitis model (Mouse)	Improves colon damage in an animal disease model and has immunosuppressive effects *in vitro*	Ma *et al*[46], 2019
Autoimmune uveitis	+	Autoimmune uveitis model (Rat)	Ameliorates autoimmune uveitis by inhibiting the migration of inflammatory cells	Bai *et al*[47], 2017
Idiopathic macular hole	-	Clinical patients (5)	May improve anatomic and visual outcomes of surgery for that disease	Zhang *et al*[48], 2018
Myocardial infarction	+	Myocardial infarction model (Rat)	UcMSC-Ex encapsulated in a functional peptide hydrogel could be effective for cardiac regeneration	Han *et al*[50], 2019

UcMSC-Ex: Exosomes derived from umbilical cord mesenchymal stem cells.

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