

MSC Exosomes

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History

MSC-derived exosomes are vesicles (small droplets with aqueous interior encapsulated by a lipid bilayer) which are released by mesenchymal stem cells (MSCs). These cells form the basis of the “mesenchymal layer” of the body, which includes bones, cartilage, muscles and connective tissue. These stem cells can differentiate into cell types that are characteristic of the tissue types (e.g. osteoblasts for bone tissue, chondrocytes for cartilage and myocytes for muscle cells). The size of MSC exosomes ranges from 30-150 nm. The primary function of MSCs is to respond to injury and infection by secreting and recruiting a range of biological factors, as well as modulating inflammatory processes to facilitate tissue repair and regeneration. They stem directly from the cell membranes of the stem cells,

which release the exosomes from their internal cellular vesicle storage.¹

The advantages of exosome utilization, when compared to their cellular counterparts, include a higher safety profile mainly due to their nanoscale size. In contrast to cells, which have a diameter of 30–60 μm , the exosomes can transfer efficiently to specific tissues after administration without aggregation.

MSCs have been known exist for several decades. However, specific research on the therapeutic potential of their exosomes only began in the early 2010s.² The idea that exosomes could play a part in cell signaling and repair preceded the confirmation by a few years.³

Since then, MSC exosomes have received a large amount of attention, with numerous studies and reviews.

Mechanism of Action

A MSC exosomes exert their biological effects primarily through intercellular communication mediated by their rich cargo of bioactive molecules, including proteins, lipids, mRNA, and microRNA (miRNA). After being released from MSCs, exosomes interact with target cells via receptor–ligand binding, membrane fusion, or endocytosis. Once internalized, their contents modulate signaling pathways in recipient cells. A key mechanism involves the transfer of miRNAs that regulate gene expression post-transcriptionally, often leading to suppression of pro-inflammatory genes and activation of regenerative pathways. This enables MSC exosomes to influence cellular behavior without direct cell transplantation.⁴ More than 300 proteins and 150 microRNAs have been found in MSC exosomes in

addition to other bioactive molecules.⁵⁻⁹

A major functional mechanism of MSC exosomes is immunomodulation. Their cargo can suppress excessive immune responses by inhibiting the proliferation and activation of T cells, promoting regulatory T cell (Treg) expansion, and shifting macrophages from a pro-inflammatory (M1) to an anti-inflammatory (M2) phenotype.

This is mediated through signaling pathways such as NF- κ B, STAT3, and PI3K/Akt.

Additionally, exosomes carry anti-inflammatory cytokines and regulatory miRNAs (e.g., miR-146a, miR-21), which further dampen inflammatory signaling. Through these coordinated actions, MSC exosomes help restore immune homeostasis in conditions such as autoimmune diseases and tissue injury.¹⁰

MSC-derived exosomes also promote tissue repair and regeneration by enhancing angiogenesis, reducing apoptosis, and stimulating proliferation of resident cells. They deliver growth factors (such as VEGF and TGF- β) and pro-angiogenic miRNAs that activate endothelial cells and support new blood vessel formation. Simultaneously, they protect damaged cells by modulating apoptotic pathways, often through upregulation of anti-apoptotic proteins like Bcl-2 and downregulation of pro apoptotic factors such as Bax. These regenerative effects are complemented by their ability to remodel the extracellular matrix and activate stem/progenitor cells

in injured tissues, making MSC exosomes a promising cell-free therapeutic strategy in regenerative medicine.

Preclinical Studies

Cell Culture

A study in human cell culture found that MSC exosomes can activate human brain microvascular cells and promote the formation of new blood vessels. A molecule involved in this mechanism was found to be ICAM1, a known factor necessary for white blood cell migration through blood vessel walls. It was concluded that MSC exosomes may be useful in some disorders stemming from brain blood circulation, most prominently vascular dementia.¹¹

Using chondrocyte cultures, the authors of a 2018 study could attribute the rapid cellular proliferation and infiltration during exosome-mediated cartilage repair to specific exosome-initiated pathways. The exosomes-treated tissues also displayed a regenerative immune phenotype characterized by a higher infiltration of M2 macrophages (which is a macrophage subtype associated with tissue repair) and with a concomitant reduction in pro-inflammatory cytokines IL-1 β and TNF- α .

Together, these observations demonstrated that the efficient regeneration by MSC exosomes was affected through a coordinated mobilization of multiple cell types and activation of several cellular processes.¹² An additional study using

chondrocytes came to similar conclusions and further elucidates molecular mechanisms.^{13,14} In addition to cartilage healing, MSC exosomes also showed beneficial effects in bone healing in mice.¹⁵

Multiple studies have shown significant interactions of cancer cells with MSC exosomes. They generally show fusion of the exosomes with the cancer cells resulting in functional changes of the cancer cells. Together, these findings demonstrated that the internalization of MSC-derived exosomes was associated with the acquisition of new tumor cell properties by altering cellular functionalities and providing the capability to re-organize the tumor microenvironment and hence a potential application in cancer therapy.¹⁶

As an alternative approach to regular MSC exosomes application to cancer cells, the exosomes can also be loaded with classical cancer therapeutics, such as taxanes.

The resulting loaded exosomes showed a much greater growth inhibition in cancer cells compared to regular MSC exosomes.¹⁷ Recent studies have reported conflicting findings regarding the effect of MSC-derived exosomes on tumors. Some studies have suggested that MSC-derived exosomes can promote tumor growth and metastasis, but others have reported that they can inhibit tumor cell growth.¹⁸ These findings are likely due to the large variety of cancer biology and cell lines. A general anti-cancer effect of MSC exosomes cannot be

expected.

Animal Experiments

In a preclinical model with rats, childbirth injury was simulated in order to investigate whether MSC exosomes could potentially be used to treat childbirth injuries in humans. It was found that the stems cells and their secretions (exosomes) were both equally effective in healing nerve and muscle injuries in the rats and both groups had significantly better tissue regeneration compared to rats treated only with saline.¹⁹

In one of the earlier studies, it was first shown that MSCs secrete substances that aided in tissue repair after damage to the heart tissue of mice.²⁰

In mice with induced stroke, MSCs and MSC exosomes both improved neurological impairment and long-term neuroprotection associated with enhanced blood vessel and neuronal growth were noticed in stroke mice receiving EVs from two different bone marrow-derived MSC lineages. Exosome administration closely resembled responses to MSCs and persisted throughout the observation period. Although cerebral immune cell infiltration was not affected by exosomes, post ischemic immunosuppression (i.e., B-cell, natural killer cell, and T-cell lymphopenia) was attenuated in the peripheral blood at 6 days after ischemia, providing an appropriate external milieu for successful brain remodeling.²¹

Moreover, MSC exosomes can exert immunomodulatory effects

in animal models of autoimmune diseases, such as multiple sclerosis,²² rheumatoid arthritis²³,²⁴, and type 1 diabetes.²⁵ Furthermore, MSC exosomes are effective in cardiac, hepatic, and renal regeneration.^{26, 27, 28}

In summary, the demonstrated efficacy of MSC exosomes in animal disease models suggests that MSC exosomes may provide a promising therapeutic approach for a variety of diseases in human.

An additional interesting preclinical finding was that MSC exosomes showed anti inflammatory activity when they were applied intranasally. The exosomes were reported to reach the hippocampus of mice with induced epilepsy within 6 hours and significantly reduced inflammation and neuron death.²⁹

The potential application of MSC exosomes in cartilage and joint repair which was known from cell culture studies was later confirmed by experiments on rats. The animals received 10 µg of exosomes into their joints. Generally, exosome-treated defects showed enhanced gross appearance and improved histological scores than the contralateral defects which were only injected with saline buffer. By 12 weeks, exosome-treated defects displayed complete restoration of cartilage and subchondral bone with characteristic features including a hyaline cartilage with good surface regularity, complete bonding to adjacent cartilage, and extracellular matrix deposition that closely resemble that of age-matched unoperated control. In

contrast, there were only fibrous repair tissues found in the control defects.³⁰

A widespread problem with biologically derived therapeutics is a harder quality control and reproducibility compared to chemically synthesized molecules. A similar problem also seems to exist with MSC exosomes. The biological function of MSC exosomes from different sources shares most properties; however, they may also vary in functionality.^{31, 32} For example, MSC exosomes extracted from adipose tissues have a better angiogenic capability than those extracted from the bone marrow.³³

Some of the studies on MSC exosomes are also therefore focused on the production of the exosomes in high purity and consistent results.³⁴

Clinical Studies

In one of the earliest trials in humans, forty chronic kidney disease patients stage III and IV have been divided into two groups; twenty patients as treatment group "A" and twenty patients as a matching placebo group "B". Two doses of MSC-derived exosomes had been administered to patients of group "A". Blood urea, serum creatinine, urinary albumin creatinine ratio (UACR) and estimated glomerular filtration rate (eGFR) have been used to assess kidney functions and TNF-α, TGF-β1 and IL-10 have been used to assess the amelioration of the inflammatory immune activity. Participants in group A exhibited significant improvement of kidney function,

serum creatinine level, blood urea and UACR. Patients of the treatment group "A" also exhibited significant increase in plasma levels of TGF- β 1, and IL-10 (two anti inflammatory cytokines) and significant decrease in plasma levels of TNF- α .

Participants of the control group B did not show significant improvement in any of the previously mentioned parameters at any time point of the study period.³⁵

The skin brightening efficacy of a cosmetic formulation containing MSC exosomes was assessed in human volunteers with hyperpigmentation in a prospective, split face, double-blind, randomized placebo-controlled study. A topical application of the MSC exosome-containing formulation statistically decreased the melanin contents compared to the placebo control. However, the melanin-reduction activity was limited and diminished along with time. The authors concluded that a further improvement in efficient transdermal delivery of MSC exosomes would be helpful for more profound efficacy.³⁶

In another study with topical treatment, a total of 25 patients received 3 consecutive treatment sessions of fractional CO2 laser to the whole face, with a follow-up evaluation. Post-laser treatment regimens were applied; for each patient, one side of the face was treated with adipose tissue stem cell-derived exosomes gel and the other side was treated with control gel. MSC exosome-treated sides had achieved a significantly greater improvement than the

control sides at the final follow-up visit.

Treatment-related erythema was milder, and post-treatment downtime was shorter on the applications of human adipose tissue stem cell-derived exosomes-treated side.³⁷

Topical treatment with MSC exosomes is a potential treatment option for inflammatory skin diseases such as atopic dermatitis or psoriasis. A phase I study was performed to assess the safety and tolerability of an MSC exosome ointment, PTD2021P, for topical application in healthy adult volunteers. One subject was reported with 1 treatment-emergent adverse event of COVID-19 infection during the study. The event was moderate in severity and unlikely related to the study drug. This TEAE was resolved and the subject recovered fully. No subject was reported with clinically significant abnormality for laboratory parameters. As per the visual assessment of the area of application, no subject had dryness, itch, oozing/crusting, redness, scratch marks, skin thickening, sleeplessness, or swelling at the area of application of skin.³⁸

MSC exosomes were also investigated in critically ill COVID-19 patients (NCT04657458). Patient survival rate was 83%; about 71% of the patients were cured, 13% remained in critical but stable condition, and 16% died for reasons unrelated to the treatment.³⁹

A first report on a commercial product formulation of MSC

exosomes MSC exosome product (ExoFlo™) to treat osteoarthritis (OA). Thirty-three Navy SEAL veterans were treated with ExoFlo for OA of the knee (n=58), shoulder (n=32), elbow (n=16), hip (n=12), ankle (n=8) or wrist (n=6). At six-month follow-up, the average patient improved in pain severity and limb functionality. Ninety-five percent of the improvement occurred within the first six weeks following injection. There were no complications or adverse events, minor or major, and no patient was observed to have accelerated OA progression resultant from the ExoFlo injection. These patients will continue to be followed for at least 2-years. At six-month follow-up, a single ExoFlo injection for OA appears safe and clinically efficacious for the treatment of patients with medium to severe grade osteoarthritis.⁴⁰

Another study in humans sought to explore the potential of MSC exosomes to be inhaled, possibly laying the groundwork for treatment of inflammatory lung and airway disease. Twenty-four healthy volunteers were involved and received the MSC exosomes once, ranging from 2×10^8 particles to 16×10^8 particles (MEXVT study, NCT04313647). All volunteers tolerated the MSC exosome nebulization well, and no serious adverse events were observed from starting nebulization to the 7th day after nebulization. These findings suggest that nebulized MSC exosomes could be a promising therapeutic strategy, offering preliminary evidence to promote the future clinical applications of

nebulized MSC exosomes in lung injury diseases.⁴¹

Conclusion

MSC exosomes have been an immensely popular topic in the last 15 years in regenerative medicine. From the available evidence, they show a number of effects in animals and humans. Effects of MSC exosomes can be classified in the following categories:

- Pro-angiogenic
- Anti-inflammatory
- Immunomodulatory, with a tendency to reduce immune activity
- Anti-apoptotic
- Anti-fibrotic
- Anti-oxidant

They are also flexible in their application form. MSC exosomes have been shown to be effective via i.v. infusion, intranasally, via inhalation and direct joint injection. From early clinical trials, there is no evidence of toxicity or other adverse events associated with MSC exosome treatment.

In a substantial amount of research on cell cultures and animals shows promising results which indicate that MSC exosomes could be useful to treat a variety of inflammatory and age-related conditions.

Currently, there is an extraordinary amount of interest in treating human diseases using MSC exosomes. In 2023 alone, at least 150 clinical trials were registered that investigated exosome-based therapies for a

variety of conditions, including respiratory diseases, infectious diseases, and cancer.⁴² Most of these studies have not been completed and reported by now (March 2026), but it can be expected that there will be a lot more clinical data about MSC exosomes in the coming years.

Further Reading

[Combined Therapy With Simvastatin and Bone Marrow-Derived Mesenchymal Stem Cells Increases Benefits in Infarcted Swine Hearts \(2008\)](#)

[MSC-derived exosomes: a novel tool to treat therapy-refractory graft-versus-host disease \(2014\)](#)

[Exosomes Derived from Mesenchymal Stem Cells \(2014\)](#)

[Exosomes from bone marrow mesenchymal stem cells contain a microRNA that promotes dormancy in metastatic breast cancer cells \(2014\)](#)

[Engineered mesenchymal stem cells with enhanced tropism and paracrine secretion of cytokines and growth factors to treat traumatic brain injury \(2015\)](#)

[Mesenchymal stem cell exosomes \(2015\)](#)

[MSC exosome as a cell-free MSC therapy for cartilage regeneration: Implications for osteoarthritis treatment \(2017\)](#)

[Concise Review: MSC-Derived Exosomes for Cell-Free Therapy \(2017\)](#)

[Mesenchymal stem cell-derived exosomes as a new therapeutic strategy for liver diseases \(2017\)](#)

[Potential Effects of MSC-Derived Exosomes in Neuroplasticity in Alzheimer's Disease \(2018\)](#)

[MSC-exosome: A novel cell-free therapy for cutaneous regeneration \(2018\)](#)

[MSC-Derived Exosomes-Based Therapy for Peripheral Nerve Injury: A Novel Therapeutic Strategy \(2019\)](#)

[Exosomes from mesenchymal stem/stromal cells: a new therapeutic paradigm \(2019\)](#)

[Mesenchymal stem cell-derived exosomes for clinical use \(2019\)](#)

[Mesenchymal Stromal Cells and Exosomes: Progress and Challenges \(2020\)](#)

[Dual Role of MSC-Derived Exosomes in Tumor Development \(2020\)](#)

[Bioengineered MSC-derived exosomes in skin wound repair and regeneration \(2023\)](#)

["Mesenchymal stem cell-derived exosomes \(MSC-exosomes\) in hematology: From mechanisms to clinical breakthroughs" \(2025\)](#)

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