

Mesenchymal Stem Cells-Derived Exosomes: A Possible Therapeutic Strategy for Osteoporosis.

[Li Y](#)¹, [Jin D](#)², [Xie W](#)², [Wen L](#)¹, [Chen W](#)¹, [Xu J](#)², [Ding J](#)², [Ren D](#)¹, [Xiao Z](#)¹.

[Author information](#)

Abstract

Osteoporosis is a common age-related disorder characterized by low bone mass and deterioration in bone microarchitecture, leading to increased skeletal fragility and fracture risk. The pathophysiology of osteoporosis is multifactorial. It is related to the imbalance between osteoblasts and osteoclasts; reduced bone mass and increased adipogenesis in the bone marrow. Moreover, angiogenesis, inflammatory process and miRNAs have shown effects in the formation of osteoporosis. In the recent years, mesenchymal stem cells (MSCs) have been regarded as an excellent choice for cell-based tissue engineering therapy of osteoporosis. Growing evidence showed that, paracrine effect have been considered as the predominant mechanism for the role of MSCs in tissue repair. Recently, many studies have proposed that MSCs-derived exosomes are effective for a variety of diseases like cancer, cardiovascular diseases, etc. However, whether the MSCs-derived exosomes could serve as a novel therapeutic tool for osteoporosis has not clearly described. In this review, we summarize the MSCs-derived exosomes and the relationship with osteogenesis, osteoclast differentiation, angiogenesis, immune processes and miRNAs. Finally, we suggest that MSCs-derived exosomes might be a promising therapeutic method for osteoporosis in the future.

[Mult Scler J Exp Transl Clin.](#) 2018 Mar 26;4(1):2055217318765288. doi: 10.1177/2055217318765288.

eCollection 2018 Jan-Mar.

Feasibility of mesenchymal stem cell culture expansion for a phase I clinical trial in multiple sclerosis.

[Planchon SM](#)¹, [Lingas KT](#)², [Reese Koç J](#)², [Hooper BM](#)², [Maitra B](#)², [Fox RM](#)², [Imrey PB](#)^{1,3}, [Drake KM](#)⁴, [Aldred MA](#)⁴, [Lazarus HM](#)², [Cohen JA](#)¹.

[Author information](#)

Abstract

BACKGROUND:

Multiple sclerosis is an inflammatory, neurodegenerative disease of the central nervous system for which therapeutic mesenchymal stem cell transplantation is under study. Published experience of culture-expanding multiple sclerosis patients' mesenchymal stem cells for clinical trials is limited.

OBJECTIVE:

To determine the feasibility of culture-expanding multiple sclerosis patients' mesenchymal stem cells for clinical use.

METHODS:

In a phase I trial, autologous, bone marrow-derived mesenchymal stem cells were isolated from 25 trial participants with multiple sclerosis and eight matched controls, and culture-expanded to a target single dose of $1-2 \times 10^6$ cells/kg. Viability, cell product identity and sterility were assessed prior to infusion. Cytogenetic stability was assessed by single nucleotide polymorphism analysis of mesenchymal stem cells from 18 multiple sclerosis patients and five controls.

RESULTS:

One patient failed screening. Mesenchymal stem cell culture expansion was successful for 24 of 25 multiple sclerosis patients and six of eight controls. The target dose was achieved in 16-62 days, requiring two to three cell passages. Growth rate and culture success did not correlate with demographic or multiple sclerosis disease characteristics. Cytogenetic studies identified changes on one chromosome of one control (4.3%) after extended time in culture.

CONCLUSION:

Culture expansion of mesenchymal stem cells from multiple sclerosis patients as donors is feasible. However, culture time should be minimized for cell products designated for therapeutic administration.

[Cytotherapy](#). 2018 Apr 2. pii: S1465-3249(18)30408-0. doi: 10.1016/j.jcyt.2018.02.372. [Epub ahead of print]

Mesenchymal stromal cell exosome-enhanced regulatory T-cell production through an antigen-presenting cell-mediated pathway.

[Zhang B](#)¹, [Yeo RWY](#)², [Lai RC](#)¹, [Sim EWK](#)¹, [Chin KC](#)³, [Lim SK](#)⁴.

Author information

Abstract

BACKGROUND AIMS:

The immunomodulatory property of mesenchymal stromal cell (MSC) exosomes is well documented. On the basis of our previous report that MSC exosomes increased regulatory T-cell (Treg) production in mice with allogenic skin graft but not in ungrafted mice, we hypothesize that an activated immune system is key to exosome-mediated Treg production.

METHODS:

To test our hypothesis, MSC exosomes were incubated with mouse spleen CD4⁺ T cells that were activated with either anti-CD3/CD28 mAbs or allogenic antigen-presenting cell (APC)-enriched spleen CD11c⁺ cells to determine whether production of mouse CD4⁺CD25⁺ T cells or CD4⁺CD25⁺Foxp3⁺ Tregs could be induced. MSC exosomes were also administered to the lethal chimeric human-SCID mouse model of graft-versus-host disease (GVHD) in which human peripheral blood mononuclear cells were infused into irradiated NSG mice to induce GVHD.

RESULTS:

We report here that MSC exosome-induced production of CD4⁺CD25⁺ T cells or CD4⁺CD25⁺Foxp3⁺ Tregs from CD4⁺ T cells activated by allogeneic APC-enriched CD11C⁺ cells but not those activated by anti-CD3/CD28 mAbs. This induction was exosome- and APC dose-dependent. In the mouse GVHD model in which GVHD was induced by transplanted human APC-stimulated human anti-mouse CD4⁺ T cell effectors, MSC exosome alleviated GVHD symptoms and increased survival. Surviving exosome-treated mice had a significantly higher level of human CD4⁺CD25⁺CD127^{low/-} Tregs than surviving mice treated with Etanercept, a tumor necrosis factor inhibitor.

[J Control Release](#). 2018 Apr 2. pii: S0168-3659(18)30173-1. doi: 10.1016/j.jconrel.2018.03.034. [Epub ahead of print]

Mesenchymal stem cells encapsulated into biomimetic hydrogel scaffold gradually release CCL2 chemokine in situ preserving cytoarchitecture and promoting functional recovery in spinal cord injury.

[Papa S¹](#), [Vismara I¹](#), [Mariani A²](#), [Barilani M³](#), [Rimondo S⁴](#), [De Paola M²](#), [Panini N⁵](#), [Erba E⁵](#), [Mauri E⁴](#), [Rossi F⁴](#), [Forloni G¹](#), [Lazzari L⁶](#), [Veqlianese P⁷](#).

Author information

Abstract

Spinal cord injury (SCI) is an acute neurodegenerative disorder caused by traumatic damage of the spinal cord. The neuropathological evolution of the primary trauma involves multifactorial processes that exacerbate the pathology, worsening the neurodegeneration and limiting neuroregeneration. This complexity suggests that multi-therapeutic approaches, rather than any single treatment, might be more effective. Encouraging preclinical results indicate that stem cell-based treatments may improve the disease outcome due to their multi-therapeutic ability. Mesenchymal Stem Cells (MSCs) are currently considered one of the most promising approaches. Significant improvement in the behavioral outcome after MSC treatment sustained by hydrogel has been demonstrated. However, it is still not known how hydrogel contribute to the delivery of factors secreted from MSCs and what factors are released in situ. Among different mediators secreted by MSCs after seeding into hydrogel, we have found CCL2 chemokine, which could account for the neuroprotective mechanisms of these cells. CCL2 secreted from human MSCs is delivered efficaciously in the lesioned spinal cord acting not only on recruitment of macrophages, but driving also their conversion to an M2 neuroprotective phenotype. Surprisingly, human CCL2 delivered also plays a key role in preventing motor neuron degeneration in vitro and after spinal cord trauma in vivo, with a significant improvement of the motor performance of the rodent SCI models.

[Cell Commun Signal](#). 2018 Apr 6;16(1):13. doi: 10.1186/s12964-018-0225-2.

Interaction between human osteosarcoma and mesenchymal stem cells via an interleukin-8 signaling loop in the tumor microenvironment.

[Kawano M¹](#), [Tanaka K²](#), [Itonaga I¹](#), [Iwasaki T¹](#), [Tsumura H¹](#).

Author information

Abstract

BACKGROUND:

Osteosarcoma (OS) is the representative primary malignant bone tumor with the highest incidence. It is known that malignant phenotypes of OS, such as proliferation, invasion, and metastasis, are significantly influenced not only by characteristics of the tumor itself, but also by the surrounding microenvironment. In other words, OS is considered to utilize cells in the vicinity of the tumor by changing the characteristics of these cells. Direct intercellular contact is believed to be important for this phenomenon. In the present study, we hypothesized that an interaction mediated by a humoral factor, requiring no cellular contact, might play a significant role in the progression of OS.

METHODS:

We developed a new co-culture model, using OS cells and mesenchymal stem cells (MSCs) without cellular contact, and found that both cell types expressed IL-8 at a high level, and FAK in OS cells was phosphorylated leading to an increase in the metastatic potential of the tumor in the co-culture condition.

RESULTS:

It was revealed that OS cells formed a loop of signal cross-talk in which they released IL-8 as a paracrine factor, stimulating MSCs to express IL-8, and received IL-8 released by MSCs to accelerate IL-8 expression in OS cells. Administration of anti-IL-8 antibody resulted in the inhibition of FAK expression, its downstream signaling, and the invasive potential of the OS cells, resulting in decrease in metastatic lesions.

CONCLUSION:

The present study might lead not only to the clarification of a new molecular mechanism of invasion and metastasis of OS, but also to the development of a new therapeutic strategy of blocking IL-8 in OS.