

Cytotherapy

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Mesenchymal Stem Cells in the Treatment of Articular Cartilage Degeneration: New Biological Insights for an Old-Timer Cell

[Alessandra Colombini](#), [Carlotta Perucca Orfei](#) ... [Laura de Girolamo](#)expand

- PMID: 31784241
- DOI: [10.1016/j.jcyt.2019.10.004](https://doi.org/10.1016/j.jcyt.2019.10.004)

Abstract

Osteoarthritis (OA) is a debilitating, degenerative joint disease characterized by progressive destruction of articular cartilage. Given the poor repair capacity of articular cartilage and the associated local destructive immune/inflammatory responses involving all joint structures, OA frequently ends up as a "whole joint failure" requiring prosthetic replacement. Current pharmacological efforts, belatedly started, mainly aim at symptomatic pain relief, underscoring the need for novel therapeutic schemes designed to modify the course of the disease. Mesenchymal stem cell (MSC)-based therapy has gained significant interest, sparking the design of multiple trials proving safety while providing promising preliminary efficacy results. MSCs possess 'medicinal signaling cell' properties related to their immunomodulatory and anti-inflammatory effects, which induce the establishment of a pro-regenerative microenvironment at the injured tissue. Those trophic effects are paralleled by the long-established chondroprogenitor capacity that can be harnessed to ex vivo fabricate engineered constructs to repair damaged articular cartilage. The present review focuses on these two aspects of the use of MSCs for articular cartilage damage, namely, cell therapy and tissue engineering, providing information on their use criteria, advancements, challenges and strategies to overcome them.

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- , 17 (1), 397
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The Impact of Cryopreservation on Bone Marrow-Derived Mesenchymal Stem Cells: A Systematic Review

[Soukaina Bahsoun](#), [Karen Coopman](#), [Elizabeth C Akam](#)[expand](#)

- PMID: 31783866
- DOI: [10.1186/s12967-019-02136-7](https://doi.org/10.1186/s12967-019-02136-7)

Abstract

Mesenchymal stem cells (MSCs) represent an invaluable asset for the field of cell therapy. Human Bone marrow-derived MSCs (hBM-MSCs) are one of the most commonly used cell types in clinical trials. They are currently being studied and tested for the treatment of a wide range of diseases and conditions. The future availability of MSCs therapies to the public will require a robust and reliable delivery process. Cryopreservation represents the gold standard in cell storage and transportation, but its effect on BM-MSCs is still not well established. A systematic review was conducted to evaluate the impact of cryopreservation on BM-MSCs and to attempt to uncover the reasons behind some of the controversial results reported in the literature. Forty-one in vitro studies were analysed, and their results organised according to the cell attributes they assess. It was concluded that cryopreservation does not affect BM-MSCs morphology, surface marker expression, differentiation or proliferation potential. However, mixed results exist regarding the effect on colony forming ability and the effects on viability, attachment and migration, genomic stability and paracrine function are undefined mainly due to the huge variabilities governing the cryopreservation process as a whole and to the lack of standardised assays.

Cells

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- , 8 (12)
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NG2 as an Identity and Quality Marker of Mesenchymal Stem Cell Extracellular Vesicles

[Mario Barilani](#), [Valeria Peli](#) ... [Lorenza Lazzari](#)expand

- PMID: 31783568
- DOI: [10.3390/cells8121524](https://doi.org/10.3390/cells8121524)

Abstract

The therapeutic potential of mesenchymal stem cell (MSC) extracellular vesicles (EV) is currently under investigation in many pathological contexts. Both adult and perinatal MSC are being considered as sources of EV. Herein, we address antigen expression of cord blood and bone marrow MSC and released EV to define an identity and quality parameter of MSC EV as a medicinal product in the context of clinical applications. The research focuses on EV-shuttled neural/glial antigen 2 (NG2), which has previously been detected as a promising surface marker to distinguish perinatal versus adult MSC. Indeed, NG2 was significantly more abundant in cord blood than bone marrow MSC and MSC EV. Ultracentrifuge-isolated EV were then challenged for their pro-angiogenic properties on an xCELLigence system as quality control. NG2⁺ cord blood MSC EV, but not bone marrow MSC EV, promote bFGF and PDGF-AA proliferative effect on endothelial cells. Likewise, they successfully rescue angiostatin-induced endothelial cell growth arrest. In both cases, the effects are NG2-dependent. These results point at NG2 as an identity and quality parameter for cord blood MSC EV, paving the way for their clinical translation.

Nanoscale

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Graphene Oxide/Alginate Composites as Novel Bioinks for Three-Dimensional Mesenchymal Stem Cell Printing and Bone Regeneration Applications

[Goeun Choe](#), [Seulgi Oh](#) ... [Jae Young Lee](#)expand

- PMID: 31782460
- DOI: [10.1039/c9nr07643c](#)

Abstract

Three-dimensional (3D) cell printing is a versatile technique enabling the creation of 3D constructs containing hydrogel and cells in the desired shape or pattern. Bioinks exhibiting appropriate mechanical properties and biological activities to support cell growth and/or differentiation toward a specific lineage play critical roles in 3D cell printing and tissue engineering applications. Herein, we explored alginate/graphene oxide (GO) composites as bioinks for their potential to improve printability, structural stability, and osteogenic activities for osteogenic tissue engineering applications. The addition of GO (0.05–1.0 mg mL⁻¹) to 3% alginate significantly enhanced the printing performances of the alginate bioink. In addition, mesenchymal stem cells (MSCs) printed with alginate/GO showed good proliferation and higher survival in an oxidative stress environment. The 3D scaffolds printed with MSCs and alginate/GO demonstrated significantly enhanced osteogenic differentiation compared with those printed with MSCs and alginate. Overall, a bioink of 3% alginate and 0.5 mg mL⁻¹ GO showed the most balanced characteristics in terms of printability, structural stability, and osteogenic induction of the printed MSCs. Alginate/GO composite bioinks will be useful for bioprinting research for various tissue engineering applications.

Stem Cells Int

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Is There a Noninvasive Source of MSCs Isolated With GMP Methods With Better Osteogenic Potential?

[Carla C G Pinheiro](#), [Alessander Leyendecker Junior](#) ... [Daniela F Bueno](#)expand

- PMID: 31781247
- PMCID: [PMC6875366](#)

- DOI: [10.1155/2019/7951696](https://doi.org/10.1155/2019/7951696)

Abstract

Background: A new trend in the treatment for alveolar clefts in patients with cleft lip and palate involves the use of bone tissue engineering strategies to reduce or eliminate the morbidity associated with autologous bone grafting. The use of mesenchymal stem cells-autologous cells obtained from tissues such as bone marrow and fat-combined with various biomaterials has been proposed as a viable option for use in cleft patients. However, invasive procedures are necessary to obtain the mesenchymal stem cells from these two sources. To eliminate donor site morbidity, noninvasive stem cell sources such as the umbilical cord, orbicularis oris muscle, and deciduous dental pulp have been studied for use in alveolar cleft bone tissue engineering. In this study, we evaluate the osteogenic potential of these various stem cell types.

Methods: Ten cellular strains obtained from each different source (umbilical cord, orbicularis oris muscle, or deciduous dental pulp) were induced to osteogenic differentiation *in vitro*, and the bone matrix deposition of each primary culture was quantified. To evaluate whether greater osteogenic potential of the established mesenchymal stem cell strains was associated with an increase in the expression profile of neural crest genes, real-time qPCR was performed on the following genes: SRY-box 9, SRY-box 10, nerve growth factor receptor, transcription factor AP-2 alpha, and paired box 3.

Results: The mesenchymal stem cells obtained from deciduous dental pulp and orbicularis oris muscle demonstrated increased osteogenic potential with significantly more extracellular bone matrix deposition when compared to primary cultures obtained from the umbilical cord after twenty-one days in culture ($p = 0.007$ and $p = 0.005$, respectively). The paired box 3 gene was more highly expressed in the MSCs obtained from deciduous dental pulp and orbicularis oris muscle than in those obtained from the umbilical cord.

Conclusion: These results suggest that deciduous dental pulp and orbicularis oris muscle stem cells demonstrate superior osteogenic differentiation potential relative to umbilical cord-derived stem cells and that this increased potential is related to their neural crest origins. Based on these observations, and the distinct translational advantage of incorporating stem cells from noninvasive tissue sources into tissue engineering protocols, greater study of these specific cell lines in the setting of alveolar cleft repair is indicated.

Stem Cells Int

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Intra-Bone Marrow Administration of Mesenchymal Stem/Stromal Cells Is a Promising Approach for Treating Osteoporosis

[Hideki Agata](#), [Yoshinori Sumita](#) ... [Izumi Asahina](#)expand

- PMID: 31781240
- PMCID: [PMC6875206](#)
- DOI: [10.1155/2019/4214281](#)

Abstract

Mesenchymal stem/stromal cells (MSCs) are known to be useful for treating local bone diseases. However, it is not known if MSCs are effective for treating systemic bone diseases, as the risk for mortality following intravenous MSC administration has hindered research progress. In this study, we compared the safety and efficacy of intra-bone marrow and intravenous administration of MSCs for the treatment of ovariectomy- (OVX-) induced osteoporosis. Cells capable of forming bone were isolated from the murine compact bones and expanded in culture. Relatively pure MSCs possessing increased potential for cell proliferation, osteogenic differentiation, and inhibition of osteoclastogenesis were obtained by magnetic-activated cell sorting with the anti-Sca-1 antibody. Sca-1-sorted MSCs were administered to OVX mice, which were sacrificed 1 month later. We observed that 22% of the mice died after intravenous administration, whereas none of the mice died after intra-bone marrow administration. With respect to efficacy, intravenous administration improved bone mineral density (BMD) by increasing bone mineral content without affecting bone thickness, whereas intra-bone marrow administration improved BMD by increasing both bone mineral content and bone thickness. These results indicate that intra-bone marrow administration of pure MSCs is a safer and more effective approach for treating osteoporosis.

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Adipose-Derived Stem Cells in Bone Tissue Engineering: Useful Tools With New Applications

[Gabriele Storti](#), [Maria Giovanna Scioli](#) ... [Valerio Cervelli](#)expand

- PMID: 31781238
- PMCID: [PMC6875209](#)
- DOI: [10.1155/2019/3673857](#)

Abstract

Adipose stem cells (ASCs) are a crucial element in bone tissue engineering (BTE). They are easy to harvest and isolate, and they are available in significant quantities, thus offering a feasible and valid alternative to other sources of mesenchymal stem cells (MSCs), like bone marrow. Together with an advantageous proliferative and differentiative profile, they also offer a high paracrine activity through the secretion of several bioactive molecules (such as growth factors and miRNAs) via a sustained exosomal release which can exert efficient conditioning on the surrounding microenvironment. BTE relies on three key elements: (1) scaffold, (2) osteoprogenitor cells, and (3) bioactive factors. These elements have been thoroughly investigated over the years. The use of ASCs has offered significant new advancements in the efficacy of each of these elements. Notably, the phenotypic study of ASCs allowed discovering cell subpopulations, which have enhanced osteogenic and vasculogenic capacity. ASCs favored a better vascularization and integration of the scaffolds, while improvements in scaffolds' materials and design tried to exploit the osteogenic features of ASCs, thus reducing the need for external bioactive factors. At the same time, ASCs proved to be an incredible source of bioactive, proosteogenic factors that are released through their abundant exosome secretion. ASC exosomes can exert significant paracrine effects in the surroundings, even in the absence of the primary cells. These paracrine signals recruit progenitor cells from the host tissues and enhance regeneration. In this review, we will focus on the recent discoveries which have involved the use of ASCs in BTE. In particular, we are going to analyze the different ASCs' subpopulations, the interaction between ASCs and scaffolds, and the bioactive factors which are secreted by ASCs or can induce their osteogenic commitment. All these advancements are ultimately intended for a faster translational and clinical application of BTE.

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Controlled Release of Naringin in GelMA-Incorporated Rutile Nanorod Films to Regulate Osteogenic Differentiation of Mesenchymal Stem Cells

[Yangjie Shao](#), [Dongqi You](#) ... [Lingqing Dong](#)expand

- PMID: 31763559
- PMCID: [PMC6868884](#)
- DOI: [10.1021/acsomega.9b02751](#)

Abstract

Naringin, a Chinese herbal medicine, has been demonstrated to concentration-dependently promote osteogenic differentiation of mesenchymal stem cells (MSCs). However, it remains a challenge to load naringin on coatings for osteogenesis and further control the release kinetics. Here, we demonstrated that the release behavior of naringin on rutile nanorod films could be controlled by either mixing naringin with gelatin methacryloyl (GelMA) before spinning onto the films or soaking the obtained GelMA-incorporated films with the naringin solution to achieve the distinct degradation-type release and diffusion-type release, respectively. We further revealed that the naringin-loaded coatings facilitated adhesion, proliferation and late differentiation, and mineralization of MSCs. Our findings provided a novel strategy to engineer the coatings with controlled release of naringin and emphasized the bioactivity of naringin for the osteogenic differentiation of MSCs.

Mater Sci Eng C Mater Biol Appl

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, 107, 110348

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Bioactive Silica Nanoparticles With Calcium and Phosphate for Single Dose Osteogenic Differentiation

[Márcia T Tavares](#), [Mariana B Oliveira](#) ... [Carlos Baleizão](#)expand

- PMID: 31761176
- DOI: [10.1016/j.msec.2019.110348](https://doi.org/10.1016/j.msec.2019.110348)

Abstract

The differentiation of adult stem cells is usually performed in vitro, by exposing them to specific factors. Alternatively, one can use nanocarriers containing such factors, to be internalized by the cells. In this work we have reduce the size of those carriers to the nanoscale, developing bioactive silica nanoparticles with diameters under 100 nm, containing calcium and phosphate ions (SiNPs-CaP). These ions, once released inside adult stem cells, induce bone cell proliferation and differentiation, and stimulate the expression of bone-related proteins in a single dose administration. The SiNPs-CaP nanomaterials were prepared through a sol-gel approach, and the ions added with a post-synthesis functionalization method. The synthesized SiNPs-CaP have narrow size distribution, good colloidal stability, and show high levels of ion incorporation. Furthermore, the SiNPs-CaP have good cytocompatibility and promote the osteogenic differentiation of human bone marrow mesenchymal stem cells (hBMSC), with alkaline phosphatase, osteopontin and osteocalcin production levels comparable to the ones obtained in standard osteogenic medium. The novel bioactive SiNPs-CaP are synthesized in a simple and fast manner and show the ability to promote osteogenic differentiation after a single dose administration, independently from external osteogenic inducers, showing great potential as carriers in bone tissue engineering applications.

Front Cell Dev Biol

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The Therapeutic Potential of Adipose Tissue-Derived Mesenchymal Stem

Cells to Enhance Radiotherapy Effects on Hepatocellular Carcinoma

[Lingyun Wu](#), [Qiuying Tang](#) ... [Senxiang Yan](#)[expand](#)

- PMID: 31781559
- PMCID: [PMC6861425](#)
- DOI: [10.3389/fcell.2019.00267](#)

Abstract

Several studies have investigated strategies to improve the clinical efficacy of radiotherapy (RT) against hepatocellular carcinoma (HCC), yet the prognosis remains poor. Human adipose tissue-derived mesenchymal stem cells (AT-MSCs), easily accessible and abundant in quantity, have represented as an attractive therapeutic tool for the stem cell-based treatment for cancer diseases. Through direct co-culture and indirect separate culture experiments, we showed that AT-MSCs could enhance inhibitory effect of RT on reducing HCC cell growth, migration and invasion in both *in vitro* and *in vivo* experiments. RNA-sequencing analysis revealed a noticeable interferon-induced transmembrane 1 (IFITM1)-induced tumor gene signature. Gain and loss of mechanistic studies indicated that mechanism was attributed to downregulated expression of signal transducer and activator of transcription 3 (STAT3) and matrix metalloproteinases (MMPs) and upregulated expression of P53 and caspases. Collectively, our findings suggest that AT-MSCs might enhance the therapeutic effects of RT on HCC, providing a rationale for AT-MSCs and RT combination therapy as a new remedy for HCC.