J Biophotonics. 2018 Nov 24:e201800035. doi: 10.1002/jbio.201800035. [Epub ahead of print]

Indocyanine Green labeling for optical and photoacoustic imaging of Mesenchymal Stem Cells after in vivo transplantation.

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Author information

Abstract

The transplantation of Mesenchymal Stem Cells (MSCs) holds great promise for the treatment of a plethora of human diseases, but new non-invasive procedures are needed to monitor the cell fate in vivo. Already largely used in medical diagnostics, the fluorescent dye Indocyanine Green (ICG) is an established dye to track limited numbers of cells by optical imaging, but it can be visualized also by Photoacoustic Imaging (PAI), which provides a higher spatial resolution than pure near infrared fluorescence imaging (NIRF). Because of its successful use in clinical and preclinical examinations, we chose ICG as PAI cell labeling agent. Optimal incubation conditions were defined for an efficient and clinically translatable MSC labeling protocol, such that no cytotoxicity or alterations of the phenotypic profile were observed, and a consistent intracellular uptake of the molecule was achieved. Suspensions of ICG-labeled cells were both optically and optoacoustically detected in vitro, revealing a certain variability in the photoacoustic spectra acquired by varying the excitation wavelength from 680 to 970 nm. Intramuscular engraftments of ICG-labeled MSCs were clearly visualized by both PAI and NIRF over few days after transplantation in the hindlimb of healthy mice, suggesting that the proposed technique retains a considerable potential in the field of transplantation-focused research and therapy. Stem cells were labeled with the FDA approved fluorescent dye Indocyanine Green (ICG), and detected by both photoacoustic and optical imaging, enabling to monitor the cell fate safely, in dual modality, and with good sensitivity and improved spatial resolution

Eur Rev Med Pharmacol Sci. 2018 Nov;22(21):7087-7104. doi: 10.26355/eurrev_201811_16241.

Osteoinductive effects of tantalum and titanium on bone mesenchymal stromal cells and bone formation in ovariectomized rats.

Lu MM[1], Wu PS, Guo XJ, Yin LL, Cao HL, Zou D.

Author information

Abstract

OBJECTIVE:

Although Tantalum (Ta) exhibits better osteoinductivity in healthy subjects when compared with titanium (Ti), the relative effects in osteoporosis remain unknown.

MATERIALS AND METHODS:

In this study, bone mesenchymal stromal cells of ovariectomized rats (OVX-rBMSCs) were seeded on Ta and Ti substrates for in vitro evaluation of cell viability, reactive oxygen species (ROS) production, alkaline phosphatase (ALP) activity, extracellular mineralization osteogenic gene and protein expression involved in bone morphogenetic protein (BMP2)/small mothers against decapentaplegic homologs 1 (Smad1) pathway. For in vivo assessment, Ta and Ti implants were embedded in femur defects of ovariectomized rats, followed by sequential fluorochrome labeling and histological staining.

RESULTS:

Compared to Ti, the Ta substrates demonstrated higher viable cell percentages (96.5 ± 0.26 vs. 88.17 ± 2.23%), lower ROS levels (65% vs. Ti), and enhanced ALP activity and extracellular matrix calcification. Reverse Transcription-Polymerase Chain Reaction and Western blot assays validated the better osteoinductive effect of Ta regarding small mothers against decapentaplegic homologs 1 (Smad1), runt-related transcription factor 2, bone morphogenetic protein (BMP2), and ALP expression at both the mRNA (1.5-2-fold) and protein (1.2-1.8-fold) levels. BMP2/Smad1 signaling over-expression or knockdown yielded significantly enhanced or deteriorated OVX-rBMSC osteogenesis on the two surfaces. In addition, the Ta group revealed more new bone formation (1.3-1.5-fold vs. Ti) and slightly better bone-implant contact (31.82 ± 4.07 vs. 25.2-3.84% at 8 weeks post-implantation, p = 0.052) without the contribution of specific surface structures.

CONCLUSIONS:

In comparison to Ti, Ta reveals better biocompatibility and osteoinductivity to OVX-rBMSCs, and the preferential Ta osteoinductivity may reflect its greater potential to trigger the BMP2/Smad1 cascade. Thus," in front of "Ta". Ta appears preferable to Ti as a bone-implant surface material under osteoporosis conditions.

Proteomics. 2018 Nov 23:e1800163. doi: 10.1002/pmic.201800163. [Epub ahead of print]

Proteomic signature of mesenchymal stromal cell-derived small extracellular vesicles.

van Balkom BW[1], Gremmels H[1], Giebel B[2], Lim SK[3].
Author information

Abstract

Small extracellular vesicles are 50-200 nm vesicles secreted by most cells. They are considered as mediators of intercellular communication, and EVs from specific cell types, in particular mesenchymal stem/stromal cells (MSCs), offer powerful therapeutic potential, and could provide a novel therapeutic strategy. They appear promising and safe (as EVs are non-self-replicating), and eventually MSC-derived EVs (MSC-EVs) may be developed to standardized, off-the-shelf allogeneic regenerative and immunomodulatory therapeutics. Promising pre-clinical data have been achieved using MSCs from different sources as EV-producing cells. Similarly, a variety EV isolation and characterization methods have been applied. Interestingly, MSC-EVs obtained from different sources and prepared with different methods show in vitro and in vivo therapeutic effects, indicating that isolated EVs share a common

potential. Here, we compare well-characterized and controlled publicly available proteome profiles of MSC-EVs to identify a common MSC-EV protein signature that might be coupled to the MSC-EVs' common therapeutic potential. This protein signature may be helpful in developing MSC-EV quality control platforms required to confirm the identity and test for the purity of potential therapeutic MSC-EVs.

J Microsc. 2018 Nov 22. doi: 10.1111/jmi.12771. [Epub ahead of print]

The 3D imaging of mesenchymal stem cells on porous scaffolds using high-contrasted x-ray computed nanotomography.

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Author information

Abstract

This study presents an X-ray computed nanotomography (nano-CT) based, high-resolution imaging technique. Thanks to a voxel resolution of 540 nm, this novel technique is suitable for observing the 3D morphology of soft biopolymeric scaffolds seeded with stem cells. A sample of highly porous collagen scaffold seeded with contrasted mesenchymal stem cells (MSC) was investigated by using lab-based nano-CT. The whole volume of the sample was analysed without its destruction. To evaluate the potential of nano-CT, a comparison measurement was done using a standard microscopy technique. Scanning electron microscopy (SEM) combined with energy dispersive X-ray analysis (EDX) established an extension and local accumulation of the contrasting agent - heavy metallic osmium tetroxide. The presented imaging technique is novel as it will help to understand better the behaviour of cells while interacting with three-dimensional biomaterials. This is crucial for both experimental and clinical tissue engineering applications in order to limit the risk of uncontrolled cell growth, and potentially tumour formation. LAY DESCRIPTION: Biomaterials play a crucial role in tissue engineering by serving as 3D scaffolds for cellular attachment, proliferation, and in growth ultimately leading to new tissue formation. Cell morphology and proliferation inside the 3D scaffold are necessary to know for assessing cell viability. However, these studies are usually negatively affected by the limitations of imaging techniques. We demonstrate that X-ray computed nanotomography (nano-CT), based on high-resolution imaging technique providing voxel resolution of 540 nm, is a suitable method for observing the 3D morphology of soft biopolymeric scaffolds seeded with stem cells. A sample of highly porous collagen scaffold seeded with contrasted mesenchymal stem cells (MSC) was investigated by using a lab-based nano-CT. The whole volume of the sample was analysed without its destruction. To evaluate the potential of nano-CT, a comparison measurement was done using a standard microscopy technique. Scanning electron microscopy in a combination with energy dispersive X-ray analysis established an extension and local accumulation of the contrasting agent - heavy metallic osmium tetroxide. The presented imaging technique is novel as it will help to understand better the behaviour of cells while interacting with three-dimensional biomaterials. This is crucial for both experimental and

clinical tissue engineering applications in order to limit the risk of uncontrolled cell growth, and potentially tumour formation.

J Mol Neurosci. 2018 Nov 22. doi: 10.1007/s12031-018-1216-x. [Epub ahead of print]

Mesenchymal Stem Cells from Nucleus Pulposus and Neural Differentiation Potential: a Continuous Challenge.

Lazzarini R[1], Guarnieri S[2], Fulgenzi G[3], Mariggiò MA[2], Graciotti L[3], Martiniani M[4], Orciani M[5], Specchia N[4], Di Primio R[1].
Author information

Abstract

Mesenchymal stem cells (MSCs) are well-characterized adult stem cells, recently isolated from human nucleus pulposus of degenerate and non-degenerate intervertebral disc. The attention to this source is linked to its embryologic history and cells may conserve a stronger aptitude to neuronal differentiation than other MSCs. Here, MSCs from nucleus pulposus (NP-MSCs) were successfully isolated and characterized for morphology, proliferation, and expression of selected genes. Subsequently, the neuronal differentiation was induced by 10 days of culture with a neuronal medium. NP-MSCs subjected to neural differentiation media (NP-MSCs-N) showed a morphological and biochemical modifications. NP-MSCs-N displayed elongated shape with protrusion, intermediate filaments, microtubules, and electron dense granules and the ability to form neurospheres. Even if they expressed neural markers such as NESTIN, β-TUBULIN III, MAP-2, GAP-43, and ENOLASE-2, the neural differentiated cells did not show neither spontaneous nor evoked intracellular calcium variations compared to the undifferentiated cells, suggesting that cells do not have electric functional properties. Further studies are required in order to get a better understanding and characterization of NP-MSCs and analyzed the molecular mechanisms that regulate their neural differentiation potential.

Clin Sports Med. 2019 Jan;38(1):61-78. doi: 10.1016/j.csm.2018.08.004.

Adipose-Derived Stem Cell Treatments and Formulations.

Di Matteo B[1], El Araby MM[2], D'Angelo A[3], Iacono F[2], Nannini A[2], Vitale ND[2], Marcacci M[2], Respizzi S[2], Kon E[2].
Author information

Abstract

This article analyzes the current literature on the use of adipose-derived stem cells (ASCs) to evaluate the available evidence regarding their therapeutic potential in the treatment of cartilage pathology. Seventeen articles were included and analyzed, showing that there is overall a lack of high-quality evidence concerning the use of ASCs. Most trials are case series with short-term evaluation. The most adopted approach consists of an intra-articular injection of the stromal vascular fraction (SVF) rather than the expanded cells. Based on the available data, no specific preparation method or formulation could be considered as the preferred choice in clinical practice.

Cancer Gene Ther. 2018 Nov 22. doi: 10.1038/s41417-018-0062-x. [Epub ahead of print]

Targeting GD2-positive glioblastoma by chimeric antigen receptor empowered mesenchymal progenitors.

Golinelli G[1], Grisendi G[2,3], Prapa M[2], Bestagno M[4], Spano C[2,3], Rossignoli F[2], Bambi F[5], Sardi I[6], Cellini M[7], Horwitz EM[8], Feletti A[9], Pavesi G[9], Dominici M[10,11].
Author information

Abstract

Tumor targeting by genetically modified mesenchymal stromal/stem cells (MSCs) carrying anti-cancer molecules represents a promising cell-based strategy. We previously showed that the pro-apoptotic agent tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) can be successfully delivered by MSCs to cancer sites. While the interaction between TRAIL and its receptors is clear, more obscure is the way in which MSCs can selectively target tumors and their antigens. Several neuroectoderm-derived neoplasms, including glioblastoma (GBM), sarcomas, and neuroblastoma, express high levels of the tumor-associated antigen GD2. We have already challenged this cell surface disialoganglioside by a chimeric antigen receptor (CAR)-T cell approach against neuroblastoma. With the intent to maximize the therapeutic profile of MSCs delivering TRAIL, we here originally developed a bi-functional strategy where TRAIL is delivered by MSCs that are also gene modified with the truncated form of the anti-GD2 CAR (GD2 tCAR) to mediate an immunoselective recognition of GD2-positive tumors. These bi-functional MSCs expressed high levels of TRAIL and GD2 tCAR associated with a robust anti-tumor activity against GD2-positive GBM cells. Most importantly, the anti-cancer action was reinforced by the enhanced targeting potential of such bi-functional cells. Collectively, our results suggest that a truncated anti-GD2 CAR might be a powerful new tool to redirect MSCs carrying TRAIL against GD2-expressing tumors. This affinity-based dual targeting holds the promise to combine site-specific and prolonged retention of MSCs in GD2-expressing tumors, thereby providing a more effective delivery of TRAIL for still incurable cancers.

Braz Oral Res. 2018 Nov 14;32:e83. doi: 10.1590/1807-3107bor-2018.vol32.0083.

Efficacy of stem cells on bone consolidation of distraction osteogenesis in animal models: a systematic review.

Morillo CMR[1], Sloniak MC[1], Gonçalves F[2], Villar CC[1].
Author information

Abstract

Distraction osteogenesis (DO) relies on the recruitment and proliferation of mesenchymal stem cells (MSC) to the target site, where they differentiate into osteoblasts to promote bone formation. Nevertheless, MSC recruitment appears to be slow and limits bone formation in DO defects. Thus, this systematic review aims to evaluate the ability of locally applied MSC to enhance bone formation in DO preclinical models. Databases were searched for quantitative pre-clinical controlled studies that evaluated the effect of local administration of MSC on DO bone formation. Eligible studies were identified and data regarding study characteristics, outcome measures and quality were extracted. Nine studies met the inclusion criteria. Autogenous and xenogenous MSC were used to promote DO bone formation. These included bone marrow-derived MSC, adipose tissue-derived MSC and MSC derived

from human exfoliated deciduous teeth. Meta-analysis was not possible due to heterogeneities in study designs. Local MSC implantation was not associated with adverse effects. In 4 out of the 5 studies, locally delivered undifferentiated bone-marrow MSC had a positive effect on DO bone formation. Few studies evaluated the therapeutic effects of MSC from other sources. The adjunct use of biologically active molecules or forced expression of key genes involved in osteogenesis further boosted the ability of bone-marrow MSC to promote DO bone formation. While risk of bias and heterogeneity limited the strength of this systematic review, our results suggest that the use of MSC is safe and may provide beneficial effects on DO bone formation

Photodiagnosis Photodyn Ther. 2018 Nov 17. pii: S1572-1000(18)30214-X. doi: 10.1016/j.pdpdt.2018.11.013. [Epub ahead of print]

Adipogenic differentiation of murine bone marrow mesenchymal stem cells induced by visible light via photo-induced biomodulation.

Tedesco AC[1].

Author information

Abstract

BACKGROUND:

Bone marrow mesenchymal stem cells (BM-MSCs) are undifferentiated cells that can proliferate and differentiate into specialized cells for tissue self-repair. Low-level laser (LLL) can induce biomodulatory effects such as cellular proliferation, differentiation, and migration. We investigated the biomodulatory effects of the photoactive compound chloroaluminum phthalocyanine nanoemulsion (AlClPc/NE) on the adipogenic differentiation of BM-MSCs, when combined with LLL (AlClPc/NE-LLL).

METHODS:

The BM-MSCs used in this work were isolated from green fluorescent protein-positive (GFP^+) C57BL6 mice. Cells were first treated with AlClPc/NE, a well-designed photoactive nano-drug and were then subjected to in vitro expansion, morphological and immunophenotypic characterization, and cellular cytotoxicity analysis. Subsequently, BM-MSCs were induced to differentiate into adipocytes by photo-induced biomodulation with AlClPc/NE-LLL.

RESULTS:

Our results showed that the isolated cell population was consistent with murine BM-MSCs. The cellular cytotoxicity analysis revealed that the optimal nanoemulsion dose to induce BM-MSC biomodulation was 5.0 µmol/L. Twenty-four hours following treatment with AlClPc/NE, BM-MSC were subjected to visible light irradiation of 20 mJ/cm^2 at 670 nm. Six days after photo-induced biomodulation, cells maintained high GFP expression level, and expressed detectable mRNA levels of adipogenic genes (lipoprotein lipase and PPARγ); formation of lipid vacuoles was observed, and the cells did not show any tumorigenic potential in vivo.

CONCLUSIONS:

Our results indicated that photo-induced biomodulation via visible light using AlClPc/NE and LLL can induce adipogenic differentiation of murine BM-MSCs. Therefore, cell therapy with BM-MSCs and photo-induced biomodulation may contribute to the development of new therapeutic strategies that are faster and more effective than traditional methods to trigger MSC differentiation.

In Vitro Cell Dev Biol Anim. 2018 Nov 19. doi: 10.1007/s11626-018-0307-x. [Epub ahead of print]

Butyric acid induces spontaneous adipocytic differentiation of porcine bone marrow-derived mesenchymal stem cells.

Tugnoli B[1], Bernardini C[1], Forni M[1], Piva A[1], Stahl CH[2], Grilli E[3].
Author information

Abstract

Butyric acid (BA) affects the differentiation of mesenchymal stem cells (MSC) through the activation of different transcriptional pathways. The aim of this study was to determine the effects of BA on proliferation and spontaneous differentiation of porcine bone marrow-derived MSC. Second passage MSC (n = 6) were cultured in either a basal medium (BM, DMEM + 10% FBS), or BM + 2.5 mmol/L BA (BA-2.5) or BM + 5 mmol/L BA (BA-5). Cell proliferation was significantly decreased by both BA-2.5 and BA-5 after 48 h and 72 h (- 55% and - 63%, respectively). To assess the impact of BA on spontaneous differentiation, MSC were cultured for 27 d, with complete media changes every 3 d. At day 27, cells were stained for osteocytic, chondrocytic, and adipocytic differentiation. No terminal differentiation was detected in control MSC, while accumulated small drops of lipids were stained by Oil-Red-O in BA-treated cells. The phenotypic changes were associated with changes in gene expression, determined by qPCR. Treatment with BA modulated the expression of adipocytic differentiation markers: peroxisome proliferator-activated receptor γ and CCAAT/enhancer binding protein α were significantly increased by both BA-2.5 and BA-5 throughout the study, while lipoprotein lipase and fatty acid-binding protein 4 were increased by BA-5 at day 3, and decreased by both BA-5 and BA-2.5 later throughout the study. Osteocalcin and aggrecan mRNA was reduced throughout the experiment by both doses of BA ($P < 0.05$). In conclusion, our data support that BA promotes the spontaneous differentiation of porcine bone marrow-derived MSC toward an adipocytic lineage in the absence of inducing cocktail media.

Arthroscopy. 2018 Nov 16. pii: S0749-8063(18)30616-9. doi: 10.1016/j.arthro.2018.07.028. [Epub ahead of print]

Intra-articular Mesenchymal Stem Cells in Osteoarthritis of the Knee: A Systematic Review of Clinical Outcomes and Evidence of Cartilage Repair.

Ha CW[1], Park YB[2], Kim SH[3], Lee HJ[3].

Author information

Abstract

PURPOSE:

To provide a systematic review of the clinical literature reporting the efficacy of mesenchymal stem cells (MSCs) in terms of clinical outcomes including pain and function and cartilage repair in patients with osteoarthritis.

METHODS:

We systematically reviewed any studies investigating clinical outcomes and cartilage repair after the clinical application of cell populations containing MSCs in human subjects with knee osteoarthritis through MEDLINE, EMBASE, the Cochrane Library, CINAHL, Web of Science, and Scopus. Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines were followed. Studies with a level of evidence of IV or V were excluded. Methodological quality was assessed using the Modified Coleman Methodology Score. Clinical outcomes were assessed using clinical scores, and cartilage repair was assessed using magnetic resonance imaging and second-look arthroscopy findings.

RESULTS:

A total of 17 studies that met the criteria of 50 full-text studies were included in this review, with 6 randomized controlled trials, 8 prospective observational studies, and 3 retrospective case-control studies. Among 17 studies, 8 studies used bone marrow-derived MSCs, 6 used adipose tissue-derived stromal vascular fraction, 2 used adipose tissue-derived MSCs, and 1 used umbilical cord blood-derived MSCs. All studies except 2 reported significantly better clinical outcomes in the MSC group or improved clinical outcomes at final follow-up. In terms of cartilage repair, 9 of 11 studies reported improvement of the cartilage state on magnetic resonance imaging, and 6 of 7 studies reported repaired tissue on second-look arthroscopy. The mean Modified Coleman Methodology Score was 55.5 ± 15.5 (range, 28-74).

CONCLUSIONS:

Intra-articular MSCs provide improvements in pain and function in knee osteoarthritis at short-term follow-up (<28 months) in many cases. Some efficacy has been shown of MSCs for cartilage repair in osteoarthritis; however, the evidence of efficacy of intra-articular MSCs on both clinical outcomes and cartilage repair remains limited.

LEVEL OF EVIDENCE:

Level III; systematic review of level I, II, and III studies.

Stem Cells Transl Med. 2018 Nov 19. doi: 10.1002/sctm.18-0117. [Epub ahead of print]

Mesenchymal Stem Cell Administration Attenuates Colon Cancer Progression by Modulating the Immune Component within the Colorectal Tumor Microenvironment.

François S[1,2], Usunier B[1], Forgue-Lafitte ME[3,4], L'Homme B[1], Benderitter M[1], Douay L[2,5,6,7], Gorin NC[2,5,6,7], Larsen AK[3,4], Chapel A[1,2,5].

Author information

Abstract

We here determine the influence of mesenchymal stem cell (MSC) therapy on the progression of solid tumors. The influence of MSCs was investigated in human colorectal cancer cells as well as in an immunocompetent rat model of colorectal carcinogenesis representative of the human pathology. Treatment with bone marrow (BM)-derived MSCs significantly reduced both cancer initiation and cancer progression by increasing the number of tumor-free animals as well as decreasing the number and the size of the tumors by half, thereby extending their lifespan. The attenuation of cancer progression was mediated by the capacity of the MSCs to modulate the immune component. Specifically, in the adenocarcinomas (ADKs) of MSC-treated rats, the infiltration of CD68+ monocytes/macrophages was 50% less while the presence of CD3+ lymphocytes increased almost twofold. The MSCs reprogrammed the macrophages to become regulatory cells involved in phagocytosis thereby inhibiting the production of proinflammatory cytokines. Furthermore, the MSCs decreased NK (Natural Killer) and rTh17 cell activities, Treg recruitment, the presence of CD8+ lymphocytes and endothelial cells while restoring Th17 cell activity. The expression of miR-150 and miR-7 increased up to fivefold indicating a likely role for these miRNAs in the modulation of tumor growth. Importantly, MSC administration limited the damage of healthy tissues and attenuated tumor growth following radiotherapy. Taken together, we here show that that MSCs have durable action on colon cancer development by modulating the immune component of the tumor microenvironment. In addition, we identify two miRNAs associated with the capacity of MSCs to attenuate cancer growth