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Extracellular Matrix dynamics during Mesenchymal Stem Cells Differentiation.

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Abstract

Mesenchymal stem cells (MSCs) are stromal cells that display self-renewal and multipotent differentiation capacity. The repertoire of mature cells generated ranges but is not restricted to: fat, bone and cartilage. Their potential importance for both cell therapy and maintenance of in vivo homeostasis is indisputable. Nonetheless, both their in vivo identity and use in cell therapy remain elusive. A drawback generated by this fact is that little is known about the MSC niche and how it impacts differentiation and homeostasis maintenance. Hence, the roles played by the extracellular matrix (ECM) and its main regulators namely: the Matrix Metalloproteinases (MMPs) and their counteracting inhibitors (TIMPs and RECK) upon stem cells differentiation are only now beginning to be unveiled. Here, we will focus on mesenchymal stem cells and review the main mechanisms involved in adipo, chondro and osteogenesis, discussing how the extracellular matrix can impact not only lineage commitment, but, also, their survival and potentiality. This review critically analyzes recent work in the field in an effort towards a better understanding of the roles of Matrix Metalloproteinases and their inhibitors in the above-cited events.

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A Multicentric, Open-Label, Randomized, Comparative Clinical Trial of Two Different Doses of Expanded hBM-MSCs Plus Biomaterial versus Iliac Crest Autograft, for Bone Healing in Nonunions after Long Bone Fractures: Study Protocol.

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Abstract

ORTHOUNION is a multicentre, open, comparative, three-arm, randomized clinical trial (EudraCT number 2015-000431-32) to compare the efficacy, at one and two years, of autologous human bone marrow-derived expanded mesenchymal stromal cell (hBM-MSC) treatments versus iliac crest autograft (ICA) to enhance bone healing in patients with diaphyseal and/or metaphysodiaphyseal fracture (femur, tibia, and humerus) status of atrophic or oligotrophic nonunion (more than 9 months after the acute

fracture, including recalcitrant cases after failed treatments). The primary objective is to determine if the treatment with hBM-MSCs combined with biomaterial is superior to ICA in obtaining bone healing. If confirmed, a secondary objective is set to determine if the dose of 100×10^6 hBM-MSCs is noninferior to that of 200×10^6 hBM-MSCs. The participants ($n = 108$) will be randomly assigned to either the experimental low dose ($n = 36$), the experimental high dose ($n = 36$), or the comparator arm ($n = 36$) using a central randomization service. The trial will be conducted in 20 clinical centres in Spain, France, Germany, and Italy under the same clinical protocol. The confirmation of superiority for the proposed ATMP in nonunions may foster the future of bone regenerative medicine in this indication. On the contrary, absence of superiority may underline its limitations in clinical use.

[J Cell Sci.](#) 2018 Mar 13. pii: jcs.211391. doi: 10.1242/jcs.211391. [Epub ahead of print]

Matrix elasticity regulates mesenchymal stem cell chemotaxis.

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Abstract

Efficient homing of human mesenchymal stem cells (hMSCs) is likely to be dictated by the combination of physical and chemical factors present in the microenvironment. However, the crosstalk between the physical and chemical cues remains incompletely understood. Here, we address this question by probing the efficiency of epidermal growth factor (EGF)-induced hMSC chemotaxis on substrates of varying stiffness (3, 30 and 600 kPa, respectively) inside a PDMS microfluidic device. Chemotactic speed was found to be the sum of a stiffness-dependent component and a chemotactic component. While the stiffness-dependent component scaled inversely with stiffness, the chemotactic component was stiffness-independent. Faster chemotaxis on the softest 3 kPa substrates is attributed to a combination of weaker adhesions and higher protrusion rate. While chemotaxis was mildly sensitive to contractility inhibitors, suppression of chemotaxis by the actin depolymerizing drug demonstrates the role of actin-mediated protrusions in driving chemotaxis. In addition to highlighting the collective influence of physical and chemical cues in chemotactic migration, our results suggest that hMSC homing is more efficient on softer substrates.

[Stem Cells Int.](#) 2018 Feb 20;2018:4098140. doi: 10.1155/2018/4098140. eCollection 2018.

A Nonenzymatic and Automated Closed-Cycle Process for the Isolation of Mesenchymal Stromal Cells in Drug Delivery Applications.

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Abstract

The adipose tissue is a good source of mesenchymal stromal cells that requires minimally invasive isolation procedures. To ensure reproducibility, efficacy, and safety for clinical uses, these procedures

have to be in compliant with good manufacturing practices. Techniques for harvesting and processing human adipose tissue have rapidly evolved in the last years, and Lipogems® represents an innovative approach to obtain microfragmented adipose tissue in a short time, without expansion and/or enzymatic treatment. The aim of this study was to assess the presence of mesenchymal stromal cells in the drain bag of the device by using a prototype Lipogems processor to wash the lipoaspirate in standardized condition. We found that, besides oil and blood residues, the drain bag contained single isolated cells easy to expand and with the typical characteristics of mesenchymal stromal cells that can be loaded with paclitaxel to use for drug-delivery application. Our findings suggest the possibility to replace the drain bag with a "cell culture chamber" obtaining a new integrated device that, without enzymatic treatment, can isolate and expand mesenchymal stromal cells in one step with high good manufacturing practices compliance. This system could be used to obtain mesenchymal stromal cells for regenerative purposes and for drug delivery.

[Stem Cells Int.](#) 2018 Jan 11;2018:1203717. doi: 10.1155/2018/1203717. eCollection 2018.

Gap Junctions Are Involved in the Rescue of CFTR-Dependent Chloride Efflux by Amniotic Mesenchymal Stem Cells in Coculture with Cystic Fibrosis CFBE41o- Cells.

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Abstract

We previously found that human amniotic mesenchymal stem cells (hAMSCs) in coculture with CF immortalised airway epithelial cells (CFBE41o- line, CFBE) on Transwell® filters acquired an epithelial phenotype and led to the expression of a mature and functional CFTR protein. In order to explore the role of gap junction- (GJ-) mediated intercellular communication (GJIC) in this rescue, cocultures (hAMSC : CFBE, 1 : 5 ratio) were studied for the formation of GJIC, before and after silencing connexin 43 (Cx43), a major component of GJs. Functional GJs in cocultures were inhibited when the expression of the Cx43 protein was downregulated. Transfection of cocultures with siRNA against Cx43 resulted in the absence of specific CFTR signal on the apical membrane and reduction in the mature form of CFTR (band C), and in parallel, the CFTR-dependent chloride channel activity was significantly decreased. Cx43 downregulation determined also a decrease in transepithelial resistance and an increase in paracellular permeability as compared with control cocultures, implying that GJIC may regulate CFTR expression and function that in turn modulate airway epithelium tightness. These results indicate that GJIC is involved in the correction of CFTR chloride channel activity upon the acquisition of an epithelial phenotype by hAMSCs in coculture with CF cells.

[Clin Orthop Relat Res.](#) 2018 Feb;476(2):388-397. doi: 10.1007/s11999.00000000000000033.

Stem Cells Combined With Platelet-rich Plasma Effectively Treat Corticosteroid-induced Osteonecrosis of the Hip: A Prospective Study.

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Abstract

BACKGROUND:

Randomized trials have shown the benefits of injecting bone marrow-derived mesenchymal stem cells (BmMSCs) after standard hip decompression in patients with osteonecrosis of the femoral head. However, the combination of BmMSCs and platelet-rich plasma (PRP) injected into the femoral head after decompression has not been reported previously. This study reports the results in a preliminary series of patients with osteonecrosis of the femoral head treated with BmMSCs plus PRP.

QUESTIONS/PURPOSES:

(1) What is the survivorship free from reoperation, hip arthroplasty, and femoral head collapse in a preliminary series of patients with osteonecrosis of the femoral head treated with BmMSCs plus PRP? (2) Is there a change in the degree of femoral head involvement based on modified Kerboul angle? (3) What were the scores observed for pain and function at last followup? (4) Was there a difference in survivorship free from reoperation as a function of in vitro MSC count and viability?

METHODS:

Twenty-two consecutive patients (35 hips; 11 men and 11 women) with corticosteroid-induced osteonecrosis who met study inclusion criteria were enrolled; none declined participation, and none was lost to followup, although one patient (two hips) died within a year of the procedure for reasons unrelated to it, and five patients (seven hips) did not undergo MRI at the 1-year followup. All patients had precollapse osteonecrosis, rated either University of Pennsylvania Stage 1 (n = 4) or Stage 2 (n = 31 hips). Mean age and body mass index were 43 years and 31 kg/m, respectively. Patients underwent pre- and postoperative radiographs and MRI to assess femoral head involvement using the modified Kerboul angle. Absolute cell count and colony-forming unit (CFU) assays were used to assess MSC abundance and viability of the bone marrow obtained at the time of surgery. Patients were followed at regular intervals to assess clinical response to treatment with a mean followup of 3 years (range, 2-4 years). The change in femoral head involvement was assessed with the modified Kerboul angle; the Harris hip score was used to assess clinical outcome; and conversion to THA, reoperation, and survivorship free from femoral head collapse were analyzed with the Kaplan-Meier method on a per-hip basis.

RESULTS:

Survivorship free from THA, any procedure, and femoral head collapse was 84% (95% confidence interval [CI], 75%-93%), 67% (95% CI, 55%-79%), and 93% (95% CI, 76%-98%), respectively, at 3 years postoperatively; two patients (four hips) underwent a second decompression and MSC injection for persistent pain without signs of radiographic collapse. All patients with collapse underwent THA. The mean modified Kerboul angle improved from $205^{\circ} \pm 47^{\circ}$ to $172^{\circ} \pm 48^{\circ}$ postoperatively (mean change $-30^{\circ} \pm 6^{\circ}$, $p = 0.01$). A greater proportion of patients who underwent an additional procedure had a modified Kerboul grade of 3 or 4 preoperatively (80% [four of five] versus 13% [four of 30 Grade 1 or 2;

odds ratio, 26; 95% CI, 2-296; $p = 0.005$). Preoperatively the mean Harris hip score was 57 ± 12 , which improved to 85 ± 15 (mean change 28 ± 3 , $p < 0.001$) at most recent followup. Patients undergoing a reoperation or THA had a lower mean concentration of nucleated cells/mL ($5.5 \times 10 \pm 2.8 \times 10$ cells/mL versus $2.3 \times 10 \pm 2.2 \times 10$ cells/mL, $p = 0.02$) and lower mean CFUs (13 ± 6 versus 19 ± 7 , $p = 0.04$) compared with those who did not.

CONCLUSIONS:

Core hip decompression with injection of concentrated bone marrow plus PRP improved pain and function; > 90% of hips in this series were without collapse at a minimum of 2 years. In this preliminary study, successful results were seen when nucleated cell count was high and modified Kerboul grade was low. Further randomized studies are needed to determine this procedure's efficacy versus core decompression or nonoperative treatment alone.

LEVEL OF EVIDENCE:

Level II, therapeutic study.

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Targeted release of stromal cell-derived factor-1 α by reactive oxygen species-sensitive nanoparticles results in bone marrow stromal cell chemotaxis and homing, and repair of vascular injury caused by electrical burns.

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Abstract

Rapid repair of vascular injury is an important prognostic factor for electrical burns. This repair is achieved mainly via stromal cell-derived factor (SDF)-1 α promoting the mobilization, chemotaxis, homing, and targeted differentiation of bone marrow mesenchymal stem cells (BMSCs) into endothelial cells. Forming a concentration gradient from the site of local damage in the circulation is essential to the role of SDF-1 α . In a previous study, we developed reactive oxygen species (ROS)-sensitive PPADT nanoparticles containing SDF-1 α that could degrade in response to high concentration of ROS in tissue lesions, achieving the goal of targeted SDF-1 α release. In the current study, a rat vascular injury model of electrical burns was used to evaluate the effects of targeted release of SDF-1 α using PPADT nanoparticles on the chemotaxis of BMSCs and the repair of vascular injury. Continuous exposure to 220 V for 6 s could damage rat vascular endothelial cells, strip off the inner layer, significantly elevate the local level of ROS, and decrease the level of SDF-1 α . After injection of Cy5-labeled SDF-1 α -PPADT nanoparticles, the distribution of Cy5 fluorescence suggested that SDF-1 α was distributed primarily at the injury site, and the local SDF-1 α levels increased significantly. Seven days after injury with nanoparticles injection, aggregation of exogenous green fluorescent protein-labeled BMSCs at the injury site was observed. Ten days after injury, the endothelial cell arrangement was better organized and continuous, with relatively intact vascular morphology and more blood vessels. These results

showed that SDF-1 α -PPADT nanoparticles targeted the SDF-1 α release at the site of injury, directing BMSC chemotaxis and homing, thereby promoting vascular repair in response to electrical burns.

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Cell density overrides the effect of substrate stiffness on human mesenchymal stem cells' morphology and proliferation.

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Abstract

The effect of substrate stiffness on the cellular morphology, proliferation, and differentiation of human mesenchymal stem cells (hMSCs) has been extensively researched and well established. However, the majority of these studies are done with a low seeding density where cell to cell interactions do not play a significant role. While these conditions permit an analysis of cell-substratum interactions at the single cell level, such a model system fails to capture a critical aspect of the cellular micro-environment in vivo, i.e. the cell-cell interaction via matrix deformation (i.e., strain). To address this question, we seeded hMSCs on soft poly-acrylamide (PAA) gels, at a seeding density that permits cells to be mechanically interacting via the underlying substrate. We found that as the intercellular distance decreases with the increasing seeding density, cellular sensitivity towards the substrate rigidity becomes significantly diminished. With the increasing seeding density, the cell spread area increased on a soft substrate (500 Pa) but reduced on an even slightly stiffer substrate (2 kPa) as well as on glass making them indistinguishable at a high seeding density. Not only in terms of cell spread area but also at a high seeding density, cells formed mature focal adhesions and prominent stress fibres on a soft substrate similar to that of the cells being cultured on a stiff substrate. The decreased intercellular distance also influenced the proliferation rate of the cells: higher seeding density on the soft substrate showed cell cycle progression similar to that of the cells on glass substrates. In summary, this paper demonstrates how the effect of substrate rigidity on the cell morphology and fate is a function of inter-cellular distance when seeded on a soft substrate. Our AFM data suggest that such changes happen due to local strain stiffening of the soft PAA gel, an effect that has been rarely reported in the literature so far.

[Front Physiol.](#) 2018 Feb 23;9:123. doi: 10.3389/fphys.2018.00123. eCollection 2018.

The Effects of Photobiomodulation of 808 nm Diode Laser Therapy at Higher Fluence on the in Vitro Osteogenic Differentiation of Bone Marrow Stromal Cells.

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Abstract

The literature has supported the concept of mesenchymal stromal cells (MSCs) in bone regeneration as one of the most important applications in oro-maxillofacial reconstructions. However, the fate of the

transplanted cells and their effects on the clinical outcome is still uncertain. Photobiomodulation (PBM) plays an important role in the acceleration of tissue regeneration and potential repair. The aim of this *in vitro* study is to evaluate the effectiveness of PBM with 808 nm diode laser therapy, using a flat-top hand-piece delivery system at a higher-fluence (64 J/cm²) irradiation (1 W, continuous-wave) on bone marrow stromal cells (BMSCs). The BMSCs of 3 old female Balb-c mice were analyzed. The cells were divided into two groups: irradiated group and control group. In the former the cells were irradiated every 24 h during 0 day (T0), 5 (T1), 10 (T2), and 15 (T3) days, whereas the control group was non-irradiated. The results have shown that the 64 J/cm² laser irradiation has increased the Runx-related transcription factor 2 (Runx2). Runx2 is the most important early marker of osteoblast differentiation. The higher-fluence suppressed the synthesis of adipogenic transcription factor (PPAR γ), the pivotal transcription factor in adipogenic differentiation. Also, the osteogenic markers such as Osterix (Osx) and alkaline phosphatase (ALP) were upregulated with an increase in the matrix mineralization. Furthermore, western blotting data demonstrated that the laser therapy has induced a statistically valid increase in the synthesis of transforming growth factor β 1 (TGF- β 1) but had no effects on the tumor necrosis factor α (TNF α) production. The data has statistically validated the down-regulation of the important pro-inflammatory cytokines such as interleukin IL-6, and IL-17 after 808 nm PBM exposition. An increase in anti-inflammatory cytokines such as IL-1 α and IL-10 was observed. These *in vitro* studies provide for first time the initial proof that the PBM of the 808 nm diode laser therapy with flat-top hand-piece delivery system at a higher-fluence irradiation of 64 J/cm² (1 W/cm²) can modulate BMSCs differentiation in enhancing osteogenesis.

[Leukemia](#). 2018 Feb 22. doi: 10.1038/s41375-018-0061-9. [Epub ahead of print]

Mesenchymal stem cells in multiple myeloma: a therapeutical tool or target?

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Abstract

Multiple myeloma (MM) is a malignant plasma cell (PC) disorder, characterized by a complex interactive network of tumour cells and the bone marrow (BM) stromal microenvironment, contributing to MM cell survival, proliferation and chemoresistance. Mesenchymal stem cells (MSCs) represent the predominant stem cell population of the bone marrow stroma, capable of differentiating into multiple cell lineages, including fibroblasts, adipocytes, chondrocytes and osteoblasts. MSCs can migrate towards primary tumours and metastatic sites, implying that these cells might modulate tumour growth and metastasis. However, this issue remains controversial and is not well understood. Interestingly, several recent studies have shown functional abnormalities of MM patient-derived MSCs indicating that MSCs are not just by-standers in the BM microenvironment but rather active players in the pathophysiology of this disease. It appears that the complex interaction of MSCs and MM cells is critical for MM development and disease outcome. This review will focus on the current understanding of the biological role of MSCs in MM as well as the potential utility of MSC-based therapies in this malignancy.