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Polydatin, Natural Precursor of Resveratrol, Promotes Osteogenic Differentiation of Mesenchymal Stem Cells.

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Abstract

Bone loss and fractures are consequences of aging, diseases or traumas. Furthermore the increased number of aged people, due to the rise of life expectancy, needs more strategies to limit the bone loss and regenerate the lost tissue, ameliorating the life quality of patients. A great interest for non-pharmacological therapies based on natural compounds is emerging and focusing on the oligostilbene Polydatin, present in many kinds of fruits and vegetables, when resveratrol particularly in red wines. These molecules have been extensively studied due to their antioxidant and anti-inflammatory effects, showing more recently Resveratrol the ability to enhance osteogenic differentiation and bone formation. However, the clinical applications of Resveratrol are limited due to its low bioavailability and rapid metabolism, while its natural glycosilated precursor Polydatin shows better metabolic stability and major abundance in fresh fruits and vegetables. Nevertheless the role of Polydatin on osteogenic differentiation is still unexplored. Mesenchymal stem cells (MSCs) from dental tissues, such as dental bud stem cells (DBSCs), are able to differentiate toward osteogenic lineage: thus we investigated how Resveratrol and Polydatin influence the differentiation of DBSCs, eventually affecting bone formation. Our results showed that Polydatin increases MSCs osteogenic differentiation sharing similar properties with Resveratrol. These results encourage to deepen the effects of this molecule on bone health and its associated mechanisms of action, wishing for the future a successful use in bone loss prevention and therapy.

Int J Mol Sci. 2018 Jul 15;19(7). pii: E2061. doi: 10.3390/ijms19072061.

A Non-Enzymatic Method to Obtain a Fat Tissue Derivative Highly Enriched in Adipose Stem Cells (ASCs) from Human Lipoaspirates: Preliminary Results.

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Abstract

Adipose tissue possesses phenotypic gene expression characteristics that are similar to human mesenchymal stem cells (hMSCs). Nevertheless, the multilineage potential may be inhibited, and cells may not expand adequately to satisfy the requirements of Good Manufacturing Practice (cGMP). An

autologous hMSC-enriched fat product would fulfil the void from a biomedical and clinical perspective. In this study, we suggest a novel mechanism using a closed system without enzymes, additives or other modifications, which will produce non-expanded, accessible material. This decentralized fat product, unlike unprocessed lipoaspirates, adequately encloses the vascular stroma with adipocytes and stromal stalks along with their vascular channels and lumina. This fat product contained hASCs and fewer hematopoietic elements such as lipoaspirates, which were digested enzymatically according to flow cytometric investigations, and molecular analysis also showed significant hASC uniformity within the cells of the stromal vascular tissue. Moreover, the fat product produced a higher quantity of hASCs similar to hMSCs in isolation with the typical characteristics of an osteogenic, chondrogenic and adipogenic lineage. Interestingly, these properties were evident in the non-enzymatic derived adipose tissue, as opposed to hASCs in isolation from the enzymatically digested lipoaspirates, suggesting that the aforementioned procedure may be an adequate alternative to regenerate and engineer tissue for the treatment of various medical conditions and promote efficient patient recovery.

J Stem Cells Regen Med. 2018 May 30;14(1):53-58. eCollection 2018.

Granulation tissue-derived mesenchymal stromal cells: a potential application for burn wound healing in pediatric patients.

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Abstract

Objective: Multipotential cells are mobilized into peripheral blood in response to trauma, in particular in severe burns. These cells migrate to the site of injury in response to chemotactic signals to modulate inflammation, repair damaged tissue and facilitate tissue regeneration. We evaluated the possibility of isolating and *in vitro* expand mesenchymal stromal cells (MSCs) from granulation tissue (GT) during debridement of a burn wound, as a persective strategy to improve skin regeneration. **Methods:** GT obtained from a 12-month-old burn patient was *in vitro*cultured. Expanded MCSs were characterized for morphology, immunophenotype, differentiation capacity and proliferative growth. Antifibrotic features were also evaluated. **Results:** It was possible to isolate and *in vitro* expand cells from GT with the morphology, phenotype, proliferative and differentiation capacity typical of MSC, these cells were defined as GT-MSC. GT-MSCs exhibited antifibrotic features by releasing soluble factors, this activity was superior to that observed in BM-MSC. **Conclusions:** Successful isolation and expansion of MSCs from GT is reported. Considering their functional characteristics, GT-MSCs could be considered a good candidate adjuvant therapy to improve burn wound healing, particularly in pediatrics.

Cell Oncol (Dordr). 2018 Jul 19. doi: 10.1007/s13402-018-0388-2. [Epub ahead of print]

Mutual concessions and compromises between stromal cells and cancer cells: driving tumor development and drug resistance.

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Abstract

BACKGROUND:

Various cancers have been found to be associated with heterogeneous and adaptive tumor microenvironments (TMEs) and to be driven by the local TMEs in which they thrive. Cancer heterogeneity plays an important role in tumor cell survival, progression and drug resistance. The diverse cellular components of the TME may include cancer-associated fibroblasts, adipocytes, pericytes, mesenchymal stem cells, endothelial cells, lymphocytes and other immune cells. These components may support tumor development through the secretion of growth factors, evasion from immune checkpoints, metabolic adaptations, modulations of the extracellular matrix, activation of oncogenes and the acquisition of drug resistance. Here, we will address recent advances in our understanding of the molecular mechanisms underlying stromal-tumor cell interactions, with special emphasis on basic and pre-clinical information that may facilitate the design of novel personalized cancer therapies.

CONCLUSIONS:

This review presents a holistic view on the translational potential of the interplay between stromal cells and cancer cells. This interplay is currently being employed for the development of promising preclinical and clinical biomarkers, and the design of small molecule inhibitors, antibodies and small RNAs for (combinatorial) cancer treatment options. In addition, nano-carriers, tissue scaffolds and 3-D based matrices are being developed to precisely and safely deliver these compounds.

Cell Physiol Biochem. 2018 Jul 19;48(2):773-784. doi: 10.1159/000491906. [Epub ahead of print]

Role of FGF-2 Transfected Bone Marrow Mesenchymal Stem Cells in Engineered Bone Tissue for Repair of Avascular Necrosis of Femoral Head in Rabbits.

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Abstract

BACKGROUND/AIMS:

Avascular necrosis of the femoral head (ANFH) is the focus and difficulty of orthopedic diseases. Recently, tissue engineering bone for this disease has shown a good therapeutic effect. The aim of the present study was to investigate the therapeutic effect of basic fibroblast growth factor (FGF-2) as cytokines transfected bone marrow mesenchymal stem cells (BMSCs) in constructing tissue-engineered bone for avascular necrosis of the femoral head.

METHODS:

The FGF-2 gene overexpressed lentivirus-transfected rBMSCs with xenogeneic antigen-extracted cancellous bone (XACB) to construct tissue engineered bone, and the model of early avascular necrosis of the femoral head was established by lipopolysaccharide (LPS) combined with hormone. The models were randomly divided into five groups: A (control), B (XACB), C (XACB+rBMSCs), D (XACB+rBMSCs+Lv-GFP), and E (XACB+rBMSCs+Lv-FGF-2/GFP) groups. The therapeutic effect of the tissue engineered bone for the avascular necrosis of the femoral head was evaluated by gross anatomy, X-ray examination, immunohistochemistry and H&E staining.

RESULTS:

The FGF-2 gene was transfected into rBMSCs (Multiplicity of infection [MOI] = 100) by lentivirus, and its efficiency was above 95%. The rBMSCs were successfully transfected overexpressing FGF-2 by qPCR and western blot. After tissue engineering bone implantation, X-ray examination and gross specimen observation revealed that the repair area in the E group was > 80% at six weeks, the defect was completely repaired at 12 weeks, and osteogenesis was stronger, when compared with the other groups. For the X-ray score, vascular area density and new bone formation area were higher, when compared with the other groups, and the difference was statistically significant ($P< 0.05$).

CONCLUSION:

FGF-2 gene overexpression lentivirus transfection BMSCs combined with XACB to construct tissue engineered bone can effectively promote vascular regeneration, and improve the repair effect of avascular necrosis of the femoral head.

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Proliferation, migration and differentiation potential of human mesenchymal progenitor cells derived from osteoarthritic subchondral cancellous bone.

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Abstract

Background: For regenerative therapies in the orthopedic field, one prerequisite for therapeutic success in the treatment of cartilage defects is the potential of body's own cells to migrate, proliferate and differentiate into functional cells. While this has been demonstrated for mesenchymal stem and progenitor cells (MPC) from healthy tissue sources, the potential of cells from degenerative conditions is unclear. In this study the regenerative potential of MPC derived from subchondral cancellous bone with diagnosed osteoarthritis is evaluated *in vitro*. **Methods:** OaMPC isolated from bone chips of three individual patients with Kellgren grade 3 osteoarthritis were characterized by analysis of cell surface antigen pattern. Cell proliferation was evaluated by doubling time and population doubling rate. Cell migration was assessed using a multi-well migration assay. Multi-lineage potential was evaluated by histological staining of adipogenic, osteogenic and chondrogenic markers. In addition, chondrogenic

differentiation was verified by qPCR. **Results:** OaMPC showed a stable proliferation and a typical surface antigen pattern known from mesenchymal stem cells. Cell migration of oaMPC can be induced by human blood serum. OaMPC were capable of adipogenic, osteogenic and chondrogenic differentiation comparable to MPC derived from healthy conditions. **Conclusion:** OaMPC derived from knee joints affected by osteoarthritic conditions showed regeneration potential regarding migration, proliferation and chondrogenic differentiation. This suggests that oaMPC are able to contribute to cartilage repair tissue formation.

Int J Med Sci. 2018 Jun 22;15(10):1051-1061. doi: 10.7150/ijms.25760. eCollection 2018.

Migration of mesenchymal stem cells to tumor xenograft models and *in vitro* drug delivery by doxorubicin.

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Abstract

Mesenchymal stem cells (MSCs) show therapeutic effects in various types of diseases. MSCs have been shown to migrate towards inflamed or cancerous tissues, and visualized after sacrificing the animal. MSCs are able to deliver drugs to target cells, and are an ideal candidate for cancer therapy. The purpose of this study was to track the migration of MSCs in tumor-bearing mice; MSCs were also used as drug delivery vehicles. Human breast cancer cells (MDA-MB-231) and anaplastic thyroid cancer cells (CAL62) were transduced with lentiviral particles, to express the *Renilla* luciferase and mCherry (mCherry-Rluc) reporter genes. Human bone marrow-derived MSCs were transduced with lentiviral particles, to express the firefly luciferase and enhanced green fluorescence protein (Fluc2-eGFP) reporter genes (MSC/Fluc). Luciferase activity of the transduced cells was measured by bioluminescence imaging (BLI). Further *in vitro* migration assays were performed to confirm cancer cells conditioned medium dependent MSC and doxorubicin (DOX) treated MSC migration. MSCs were loaded with DOX, and their therapeutic effects against the cancer cells were studied *in vitro*. *In vivo* MSC/Fluc migration in mice having thyroid or breast cancer xenografts was evaluated after systemic injection. Rluc activity of CAL62/Rluc (R^2=0.911), MDA-MB-231/Rluc (R^2=0.934) cells and Fluc activity of MSC/Fluc (R^2=0.91) cells increased with increasing cell numbers, as seen by BLI. eGFP expression of MSC/Fluc was confirmed by confocal microscopy. Similar migration potential was observed between MSC/Fluc and naïve MSCs in migration assay. DOX treated MSCs migration was not decreased compared than MSCs. Migration of the systemically injected MSC/Fluc cells into tumor xenografts (thyroid and breast cancer) was visualized in animal models (p<0.05) and confirmed by *ex vivo* (p<0.05) BLI. Additionally, MSCs delivered DOX to CAL62/Rluc and MDA-MB-231/Rluc cells, thereby decreasing their Rluc activities. In this study, we confirmed the migration of MSCs to tumor sites in cancer xenograft models using both *in vivo* and *ex vivo* BLI imaging. DOX-pretreated MSCs showed enhanced cytotoxic effects. Therefore, this noninvasive reporter gene (Fluc2)-based BLI may

be useful for visualizing *in vivo* tracking of MSCs, which can be used as a drug delivery vehicle for cancer therapy.

Am J Sports Med. 2018 Jul;46(9):2242-2252. doi: 10.1177/0363546518780991.

Therapeutic Efficacy of Spherical Aggregated Human Bone Marrow-Derived Mesenchymal Stem Cells Cultured for Osteochondral Defects of Rabbit Knee Joints.

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Author information

Abstract

BACKGROUND:

Engraftment and longevity of transplanted cells are crucial for stem cell-based cartilage treatment.

PURPOSE:

To determine whether cultured spherical cell masses of human bone marrow-derived mesenchymal stem cells (hBM-MSCs) could improve engraftment at defect sites and to examine their corresponding effects on osteochondral regeneration.

STUDY DESIGN:

Controlled laboratory study.

METHODS:

A cylindrical osteochondral defect (5 mm wide × 5 mm deep) was created in trochlear grooves of rabbit knees. The single-cell type of hBM-MSCs with fibrin glue, the spherical type of hBM-MSCs with fibrin glue, and cell-free fibrin glue (control) were each implanted into osteochondral defect sites. A total of 18 rabbit knees were randomly assigned to 1 of the 3 groups (3 rabbits per group). Animals were sacrificed at 6 and 12 weeks after transplantation. Repaired tissues were evaluated via gross examination, histologic examination, and immunofluorescence analysis.

RESULTS:

Transplantation with spherical hBM-MSCs exhibited superior overall osteochondral restoration when compared with the single-type group, as evidenced by well-ordered mature collagen fibrils produced during subchondral bone formation in the zonation phenomenon. Immunofluorescence analysis of osteochondral defect areas with human-specific antigen revealed a larger number of mesenchymal stem cells in the spherical-type group than the single cell-type group.

CONCLUSION:

Transplantation of spherical hBM-MSCs was better than single cells from monolayer culture in improving osteochondral regeneration.

CLINICAL RELEVANCE:

The findings demonstrate a simple strategy for enhancing the potency of stem cells required for restoration of osteochondral defects. Furthermore, this strategy may be implemented with other types of stem/progenitor cell-based therapies

Chem Sci. 2018 May 24;9(24):5394-5404. doi: 10.1039/c8sc00495a. eCollection 2018 Jun 28.

Core-shell patterning of synthetic hydrogels *via* interfacial bioorthogonal chemistry for spatial control of stem cell behavior.

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Abstract

A new technique is described for the patterning of cell-guidance cues in synthetic extracellular matrices (ECM) for tissue engineering applications. Using *s*-tetrazine modified hyaluronic acid (HA), bis-*trans*-cyclooctene (TCO) crosslinkers and monofunctional TCO conjugates, interfacial bioorthogonal crosslinking was used to covalently functionalize hydrogels as they were synthesized at the liquid-gel interface. Through temporally controlled introduction of TCO conjugates during the crosslinking process, the enzymatic degradability, cell adhesivity, and mechanical properties of the synthetic microenvironment can be tuned with spatial precision. Using human mesenchymal stem cells (hMSCs) and hydrogels with a core-shell structure, we demonstrated the ability of the synthetic ECM with spatially defined guidance cues to modulate cell morphology in a biomimetic fashion. This new method for the spatially resolved introduction of cell-guidance cues for the establishment of functional tissue constructs complements existing methods that require UV-light or specialized equipment.

Cell Transplant. 2018 Jan 1:963689718788067. doi: 10.1177/0963689718788067. [Epub ahead of print]

In vivo tracking of intravenously injected mesenchymal stem cells in an Alzheimer's animal model.

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Author information

Abstract

PURPOSE:

The purpose of this study was to investigate how intravenously injected bone marrow-derived mesenchymal stem cells (BMSCs) are distributed in the body of an Alzheimer's disease (AD) animal model.

METHODS:

Stem cells were collected from bone marrow of mice and labeled with Indium-111 (^{111}In). The ^{111}In-labeled BMSCs were infused intravenously into 3×Tg-AD mice in the AD group and non-transgenic mice (B6129SF2/J) as controls. Biodistribution was evaluated with a gamma counter and gamma camera 24 and 48 h after injecting the stem cells.

RESULTS:

A gamma count of the brain showed a higher distribution of labeled cells in the AD model than in the control group at 24 ($p = .0004$) and 48 h ($p = .0016$) after injection of the BMSCs. Similar results were observed by gamma camera imaging (i.e., brain uptake in the AD model was significantly higher than that in the control group). Among the other organs, uptake by the spleen was the highest in both groups. More BMSCs were found in the lungs of the control group than in those of the AD group.

CONCLUSIONS:

These results suggest that more intravenously infused BMSCs reached the brain in the AD model than in the control group, but the numbers of stem cells reaching the brain was very small.