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A Novel Approach for Image-guided 131I Therapy of Pancreatic Ductal Adenocarcinoma using Mesenchymal Stem Cell-mediated NIS gene delivery.

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Author information

Abstract

The sodium iodide symporter (SLC5A5/NIS) as theranostic gene would allow for non-invasive imaging of functional NIS expression and therapeutic radioiodine application. Genetically engineered mesenchymal stem cells (MSCs), based on their tumor-homing abilities, show great promise as tumor-selective NIS gene delivery vehicles for non-thyroidal tumors. Towards this clinical application, tumor specificity and efficacy of MSCs were investigated in an advanced genetically engineered mouse model of pancreatic ductal adenocarcinoma (PDAC). Syngeneic murine MSCs were stably transfected with a NIS expressing plasmid driven by the CMV-promoter (NIS-MSC). In vivo 123I-scintigraphy and 124I-PET revealed significant perchlorate-sensitive NIS-mediated radioiodide accumulation in PDAC after systemic injection of NIS MSCs. Active MSC recruitment into the tumor stroma was confirmed using NIS immunohistochemistry (IHC). A therapeutic strategy, consisting of three cycles of systemic MSC-mediated NIS delivery, followed by 131I application, resulted in a significant delay and reduction in tumor growth as compared to controls. Further, IHC analysis of α-SMA and Ki67 revealed differences in the amount and behavior of activated fibroblasts in tumors of mice injected with NIS-MSCs as compared to saline treated mice. Taken together, MSCs as NIS gene delivery vehicles in this advanced endogenous PDAC mouse model demonstrated high stromal targeting of NIS by selective recruitment of NIS-MSCs after systemic application resulting in an impressive 131I therapeutic effect.

IMPLICATIONS:

These data expand the prospect of mesenchymal stem cell-mediated radioiodine imaging-guided therapy of pancreatic cancer using the sodium iodide symporter as a theranostic gene in a clinical setting.

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Characterization of Senescence of Human Adipose-Derived Stem Cells After Long-Term Expansion.

Truong NC[1,2], Bui KH[3], Van Pham P[4,5].
Author information

Abstract

INTRODUCTION:

Since the 1980s, adipose-derived stem cells (ASCs) have become a powerful and potential source for stem cell-based therapy, regenerative medicine, and even drug delivery in cancer treatment. The development of off-the-shelf mesenchymal stem cells (MSCs), including ASCs, has rapidly advanced in recent years with several clinical trials and approved products. In this technology, ASCs should be expanded long term in order to harvest higher cell number. In this study, senescence of ASCs after long-term expansion was evaluated.

METHODS:

Human ASCs (hASCs) were isolated and cultured continuously at a density of 10^3 cells/cm^2 up to passage 15. The cells were assessed for aging via changes in the following: characteristics of MSCs, mitochondrial activity, accumulation of beta-galactosidase, and expression of tumor suppressor genes.

RESULTS:

The results showed that following in vitro expansion to the 15th passage, ASCs did not show changes in immunophenotype, except for decreased expression of CD105. However, the cells increased in size and in shape and complexity (toward the "fried egg" morphology). They also almost ceased to proliferate in passage 15. Nonetheless, they maintained in vitro differentiation potential toward osteoblasts, chondrocytes, and adipocytes. Expression of tumor suppressor genes p53 and p16 did not significantly change, while p27 was significantly downregulated. Mitochondrial activities also decreased slightly in culture from passage 5 to passage 10 and remained stable to passage 15. ASCs also showed increased accumulation of beta-galactosidase in culture, but it was negligible.

CONCLUSION:

In conclusion, hASCs exhibited some particular characteristics of aged stem cells when the number of subculture cells increased. However, up to passage 10, ASCs also retained almost all of the characteristics of MSCs.

Vet Res Commun. 2018 Sep 20. doi: 10.1007/s11259-018-9738-9. [Epub ahead of print]

Could hypoxia influence basic biological properties and ultrastructural features of adult canine mesenchymal stem /stromal cells?

Iacono E[1], Pascucci L[2], Bazzucchi C[2], Cunto M[3], Ricci F[4], Rossi B[3], Merlo B[3].
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Abstract

The aim of the present study was to compare canine adipose tissue mesenchymal stem cells cultured under normoxic (20% O_2) and not severe hypoxic (7% O_2) conditions in terms of marker expression, proliferation rate, differentiation potential and cell morphology. Intra-abdominal fat tissue samples were recovered from 4 dogs and cells isolated from each sample were cultured under hypoxic and normoxic conditions. Proliferation rate and adhesion ability were determined, differentiation towards chondrogenic, osteogenic and adipogenic lineages was induced; the expression of CD44, CD34, DLA-DQA1, DLA-DRA1 was determined by PCR, while flow cytometry analysis for CD90, CD105, CD45 and

CD14 was carried out. The morphological study was performed by transmission electron microscopy. Canine AT-MSCs, cultured under different oxygen tensions, maintained their basic biological features. However, under hypoxia, cells were not able to form spheroid aggregates revealing a reduction of their adhesivness. In both conditions, MSCs mainly displayed the same ultrastructural morphology and retained the ability to produce membrane vesicles. Noteworthy, MSCs cultivated under hypoxya revealed a huge shedding of large complex vesicles, containing smaller round-shaped vesicles. In our study, hypoxia partially influences the basic biological properties and the ultrastructural features of canine mesenchymal stem /stromal cells. Further studies are needed to clarify how hypoxia affects EVs production in term of amount and content in order to understand its contribution in tissue regenerative mechanisms and the possible employment in clinical applications. The findings of the present work could be noteworthy for canine as well as for other mammalian species.

Int J Nanomedicine. 2018 Sep 7;13:5231-5248. doi: 10.2147/IJN.S167142. eCollection 2018.

Mesenchymal stem cells loaded with paclitaxel-poly(lactic-*co*-glycolic acid) nanoparticles for glioma-targeting therapy.

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Abstract

BACKGROUND:

Mesenchymal stem cells (MSCs) possess inherent tropism towards tumor cells, and so have attracted increased attention as targeted-therapy vehicles for glioma treatment.

PURPOSE:

The objective of this study was to demonstrate the injection of MSCs loaded with paclitaxel (Ptx)-encapsulated poly(d,l-lactide-*co*-glycolide) (PLGA) nanoparticles (NPs) for orthotopic glioma therapy in rats.

METHODS:

Ptx-PLGA NP-loaded MSC was obtained by incubating MSCs with Ptx-PLGA NPs. The drug transfer and cytotoxicity of Ptx-PLGA NP-loaded MSC against tumor cells were investigated in the transwell system. Biodistribution and antitumor activity was evaluated in the orthotopic glioma rats after contralateral injection.

RESULTS:

The optimal dose of MSC-loaded Ptx-PLGA NPs (1 pg/cell Ptx) had little effect on MSC-migration capacity, cell cycle, or multilineage-differentiation potential. Compared with Ptx-primed MSCs, Ptx-PLGA NP-primed MSCs had enhanced sustained Ptx release in the form of free Ptx and Ptx NPs. Ptx transfer from MSCs to glioma cells could induce tumor cell death in vitro. As for distribution in vivo, NP-loaded fluorescent MSCs were tracked throughout the tumor mass for 2 days after therapeutic injection.

Survival was significantly longer after contralateral implantation of Ptx-PLGA NP-loaded MSCs than those injected with Ptx-primed MSCs or Ptx-PLGA NPs alone.

CONCLUSION:

Based on timing and sufficient Ptx transfer from the MSCs to the tumor cells, Ptx-PLGA NP-loaded MSC is effective for glioma treatment. Incorporation of chemotherapeutic drug-loaded NPs into MSCs is a promising strategy for tumor-targeted therapy.

Materials (Basel). 2018 Sep 19;11(9). pii: E1781. doi: 10.3390/ma11091781.

Assessment of Migration of Human MSCs through Fibrin Hydrogels as a Tool for Formulation Optimisation.

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Author information

Abstract

Control of cell migration is fundamental to the performance of materials for cell delivery, as for cells to provide any therapeutic effect, they must migrate out from the delivery material. Here the influence of fibrinogen concentration on the migration of encapsulated human mesenchymal stem cells (hMSCs) from a cell spheroid through fibrin hydrogels is tracked over time. Fibrin was chosen as a model material as it is routinely employed as a haemostatic agent and more recently has been applied as a localised delivery vehicle for potential therapeutic cell populations. The hydrogels consisted of 5 U/mL thrombin and between 5 and 50 mg/mL fibrinogen. Microstructural and viscoelastic properties of different compositions were evaluated using SEM and rheometry. Increasing the fibrinogen concentration resulted in a visibly denser matrix with smaller pores and higher stiffness. hMSCs dispersed within the fibrin gels maintained cell viability post-encapsulation, however, the migration of cells from an encapsulated spheroid revealed that denser fibrin matrices inhibit cell migration. This study provides the first quantitative study on the influence of fibrinogen concentration on 3D hMSC migration within fibrin gels, which can be used to guide material selection for scaffold design in tissue engineering and for the clinical application of fibrin sealants.

Tissue Eng Part A. 2018 Sep 20. doi: 10.1089/ten.TEA.2018.0091. [Epub ahead of print]

Optimization of the Platelet-rich Plasma Concentration for Mesenchymal Stem Cell Applications.

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Abstract

Platelet-rich plasma (PRP) and mesenchymal stem cells (MSCs) are promising tools for muscular-skeletal regeneration. However, increasing evidence has demonstrated controversial effects of PRP on the tissue regeneration. To obtain optimum PRP concentrations for MSC expansion and to accurately control osteogenic, adipocytic and chondrogenic differentiation, MSCs were exposed to PRP alone or in combination with induction medium. We found that PRPs with the platelet concentration beyond 1500×109 pl/L were preferable to promote MSC proliferation. Additionally, PRPs ranging from 200×109

to 3000×109 pl/L were capable of augmenting MSC osteogenesis and PRP with 1500×109 pl/L was most effective for MSC osteogenic differentiation. Furthermore, PRPs in low platelet concentration range just slightly promoted MSC adipogenesis, and only when the platelet concentration was beyond 1800×109 pl/L, the promoted effects were evident. Moreover, PRPs range from 1000 to 3000×109 pl/L significantly enhanced chondrogenesis of MSCs in the absence and presence of chondrogenic induction medium, and PRP with 2000×109 pl/L were more effective for MSC chondrogenesis. Further, we explored the mechanisms of PRP-induced MSCs differentiation, showing that the growth factors played a major role in this process while other unknown factors may also involved in it. At last, we measured the levels of cytokines to learn that PRP-treatment suppressed the secretion of interleukin-1β, interleukin-6 and tumor necrosis factor-α but favored the production of interleukin-10 by MSCs. In summary, our findings demonstrated that PRPs with different concentrations of platelets exerted different effects on proliferation and differentiation of MSCs, which indicated that preparing appropriate PRPs may be a precise and efficient strategy for improving MSC-based tissue regeneration.

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An in vitro comparative study of multi-sources derived mesenchymal stem cells for bone tissue engineering.

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Author information

Abstract

Mesenchymal stem cells (MSCs) have been considered as promising tools for tissue engineering and regenerative medicine. However, the optimal cell source for bone regeneration remains controversial. To better identify seed cells for bone tissue engineering, we compared MSCs from seven different tissues including four from dental origins, dental pulp stem cells (DPSCs), periodontal ligament stem cells (PDLSCs), gingival mesenchymal stem cells (GMSCs) and dental follicle stem cells (DFSCs); two from somatic origins, bone marrow derived MSCs (BM-MSCs) and adipose-derived stem cells (ADSCs) and one from birth-associated perinatal tissue umbilical cord (UCMSCs). We cultured the cells under a standardized culture condition and studied their biological characteristics. According to our results, these cells exhibited similar immunophenotype and had potential for multi-lineage differentiation. MSCs from dental and perinatal tissues proliferated more rapidly than those from somatic origins. Simultaneously, DPSCs and PDLSCs owned stronger anti-apoptotic ability under the microenvironment of oxidative stress combined with serum deprivation. In respect to osteogenic differentiation, the two somatic MSCs, BM-MSCs and ADSCs, demonstrated the strongest ability for osteogenesis as compared to PDLSCs and DFSCs, which were just a little bit weaker than the formers. However, GMSCs and UCMSCs were the most pertinacious ones to differentiate to osteoblast. We also revealed that the canonical intracellular protein kinase-based cascade signaling pathways, including PI3K/AKT, MAPK/ERK and p38 MAPK, possessed different levels of activation in different MSCs after osteoblast induction. Our conclusions suggest that PDLSCs might be a good potential alternative to BM-MSCs for bone tissue engineering.

Eur J Orthop Surg Traumatol. 2018 Sep 17. doi: 10.1007/s00590-018-2310-z. [Epub ahead of print]

A useful combination for the treatment of patellofemoral chondral lesions: realignment procedure plus mesenchymal stem cell-retrospective analysis and clinical results at 48 months of follow-up.

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Author information

Abstract

INTRODUCTION:

Osteochondral lesions of the patellofemoral joint (OLPFJ) are defects of the cartilage surface and subchondral bone, which often require surgical treatment. Reparative treatments have shown some limitations in the long-term follow-up. The one-step bone marrow-derived cells transplantation (BMDCT) achieved good to excellent results in the treatment of osteochondral lesions of the femoral condyles. The aim of this study was to report the 48-month clinical and radiological results among 28 patients with OLPFJ treated with the one-step BMDCT technique associated with the anteromedialization tibial tuberosity (AMTT).

MATERIALS AND METHODS:

Twenty-eight patients from 2010 to 2013 with OLPFJ underwent the BMDCT with the one-step technique associated with the AMTT. Clinical evaluation was performed at 6, 12, 18, 24, 36 and 48 months after surgery using the Kujala PF scale, the IKDC score and the Tegner activity scale. Eighteen lesions were located on patella and ten lesions on trochlea.

RESULTS:

The preoperative Kujala score improved from 68.2 ± 4.7 to 87.2 ± 1.2 at the mean final follow-up, while the IKDC subjective score improved from 55.1 ± 6.2 to 92.13 ± 5.5. Tegner scale showed an increase from 1.7 ± 1.3 preoperatively to 5.3 ± 2.7 at the final follow-up. MRI analysis at 24-month follow-up showed an overall good filling of the lesions.

DISCUSSION AND CONCLUSIONS:

The one-step BMDCT associated with the AMTT permitted good clinical results durable over time with a high rate of patients' satisfaction. These results confirm the validity of the one-step technique also in patellofemoral joint.

Stem Cells Int. 2018 Aug 26;2018:6726185. doi: 10.1155/2018/6726185. eCollection 2018.

Current Strategies to Generate Human Mesenchymal Stem Cells In Vitro.

Steens J[1], Klein D[1].
Author information

Abstract

Mesenchymal stem cells (MSCs) are heterogeneous multipotent stem cells that are involved in the development of mesenchyme-derived evolving structures and organs during ontogeny. In the adult organism, reservoirs of MSCs can be found in almost all tissues where MSCs contribute to the maintenance of organ integrity. The use of these different MSCs for cell-based therapies has been extensively studied over the past years, which highlights the use of MSCs as a promising option for the treatment of various diseases including autoimmune and cardiovascular disorders. However, the proportion of MSCs contained in primary isolates of adult tissue biopsies is rather low and, thus, vigorous ex vivo expansion is needed especially for therapies that may require extensive and repetitive cell substitution. Therefore, more easily and accessible sources of MSCs are needed. This review summarizes the current knowledge of the different strategies to generate human MSCs *in vitro* as an alternative method for their applications in regenerative therapy.

J Plast Reconstr Aesthet Surg. 2018 Aug 8. pii: S1748-6815(18)30270-5. doi: 10.1016/j.bjps.2018.07.028. [Epub ahead of print]

Autologous fat grafting after sarcoma surgery: Evaluation of oncological safety.

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Author information

Abstract

BACKGROUND:

The regenerative effectiveness of lipoaspirate procedures relies on the presence of mesenchymal stem cells, but the stromal microenvironment and hormonal secretions of the adipose tissue may be involved in cancer growth. Only few oncological outcome studies of fat grafting at the surgical site of malignant neoplasms of mesenchymal origin are available; none of these studies examined a series of sarcoma cases.

OBJECTIVES:

We analyzed outcome in terms of local or distant spread and overall survival to investigate the oncological safety of fat grafting in patients with sarcoma.

PATIENTS AND METHODS:

Sixty consecutive patients who had undergone 143 fat grafting procedures after surgical resection of bone and soft tissue sarcomas of the head, trunk, and limbs with clear resection margins were enrolled from 2004 to 2015 in our tertiary care center. A multidisciplinary sarcoma team administered adjuvant therapies. Patients were recurrence free at fat grafting.

RESULTS:

The overall median follow-up was 7.5 years. At follow-up after fat grafting (2.4 years), one patient had distant metastasis and two had local relapse. Kaplan-Meier analysis showed disease-free survival rate of 95.4% (CI: 89.1-100.0) at 24 months. The risk of local recurrence (LR) within 24 months was 4.6% (CI: 0.0-20.9). The probability of not having LR after fat grafting was ≥ 89.1%.

CONCLUSION:

We found no evidence of an increased cancer risk after fat grafting procedures in patients with sarcoma, but a stimulatory role of fat cannot be excluded for bone sarcomas based on the cases reported here, and further studies are therefore needed.

Cells Tissues Organs. 2018 Sep 17:1-14. doi: 10.1159/000492581. [Epub ahead of print]

Comparative Analysis of Biological and Functional Properties of Bone Marrow Mesenchymal Stromal Cells Expanded in Media with Different Platelet Lysate Content.

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Author information

Abstract

Due to their ability to induce immunological tolerance in the recipient, mesenchymal stromal cells (MSCs) have been utilized in the treatment of various hematological and immune- and inflammation-mediated diseases. The clinical application of MSCs implies prior in vitro expansion that usually includes the use of fetal bovine serum (FBS). The present study evaluated the effect of different platelet lysate (PL) media content on the biological properties of MSCs. MSCs were isolated from the bone marrow of 13 healthy individuals and subsequently expanded in three different culture conditions (10% PL, 5% PL, 10% FBS) during 4 passages. The cells cultured in different conditions had comparable immunophenotype, clonogenic potential, and differentiation capacity. However, MSC growth was significantly enhanced in the presence of PL. Cultures supplemented with 10% PL had a higher number of cumulative population doublings in all passages when compared to the 5% PL condition ($p < 0.03$). Such a difference was also observed when 10% PL and 10% FBS conditions were compared ($p < 0.005$). A statistically significant difference in population doubling time was determined only between the 10% PL and 10% FBS conditions ($p < 0.005$). Furthermore, MSCs cultured in 10% PL were able to cause a 66.9% reduction of mitogen-induced lymphocyte proliferation. Three chromosome aberrations were detected in PL conditions. Since two changes occurred in the same do nor, it is possible they were donor dependent rather than caused by the culture condition. These findings demonstrate that a 10% PL condition enables a higher yield of MSCs within a shorter time without altering MSC properties, and should be favored over the 5% PL condition.