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Biomechanical evaluation of hMSCs-based engineered cartilage for chondral tissue regeneration.

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Author information

Abstract

Articular cartilage regeneration is still an open challenge in the field of tissue engineering. Although autologous chondrocytes seeded on collagen scaffolds (CSs) have already showed interesting results in the long-term repair of chondral lesions, they are not exempt from disadvantages that could be overcome using mesenchymal stem cells (MSCs). The ability of polymeric scaffolds to support MSCs proliferation and differentiation has been widely documented. However, few studies assessed their mechanical performances and additionally performing a single mechanical test, i.e. stress-strain or stress-relaxation in compression. Articular cartilage, though, possesses unique and multifaceted mechanical properties that can be exhaustively described only implementing a complete set of mechanical tests. Hence, the final aim of this study was to in depth assess the mechanical properties of human MSCs-cultured collagen scaffolds applying unconfined stress-strain, stress-relaxation and dynamic compression tests and identify key mechanical parameters. Firstly, plain CSs were fabricated and cultured under chondrogenic conditions with human MSCs (hMSCs). CSs displayed a high-interconnected porosity permitting uniform hMSCs distribution along the scaffold depth. Within CSs, hMSCs differentiated in chondroblasts, characterized by the presence of the lacunae and by a pericellular matrix positive for GAGs and for type 2 collagen deposition. The deep implemented mechanical characterization highlighted that the engineered constructs display (i) higher resistance to compression, (ii) more marked viscoelastic behavior over time and (iii) increased dynamic properties compared to naked CSs. In particular, stress-strain testes showed significant increase in the engineered constructs' stiffness that can be related to the proteoglycan deposition, observed by histology at the end of culture. Stress-relaxation and dynamic tests pointed out a substantial increase of peak and equilibrium stresses, relaxation time and dynamic modulus in the engineered constructs compared to empty CSs, suggesting a considerable decrease in scaffold permeability due to a strong chondral matrix deposition. Overall, the obtained results indicate a significant improvement of cell/CS mechanical performance toward a cartilage-like mechanical behavior.

Regen Med. 2018 Jun;13(4):385-394. doi: 10.2217/rme-2018-0001.

Extracellular vesicles derived from mesenchymal cells: perspective treatment for cutaneous wound healing in pediatrics.

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Abstract

AIM:

We evaluated the effects of the intradermal injection of extracellular vesicles (EVs) derived from adipose stem cells (ASC-EVs) and bone marrow cells (BM-EVs) in an experimental cutaneous wound repair model.

METHODS:

Mesenchymal stem cells (MSCs) were in vitro expanded from adipose (ASC) or BM tissues (BM-MSC) of rabbits. EVs were separated from the supernatants of confluent ASC and BM-MSCs. Two skin wounds were induced in each animal and treated with MSC or EV injections. Histological examination was performed postinoculation.

RESULTS:

EV-treated wounds exhibited a better restoration compared with the counterpart MSC treatment. ASC-EV-treated wounds were significantly better than BM-EVs ($p = 0.036$).

CONCLUSION:

EV topical inoculation provides restored architecture during cutaneous wound healing and represents a promising solution for regenerative medicine in children.

Aging (Albany NY). 2018 Jul 12. doi: 10.18632/aging.101493. [Epub ahead of print]

Hybrid complexes of high and low molecular weight hyaluronan delay in vitro replicative senescence of mesenchymal stromal cells: a pilot study for future therapeutic application.

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Abstract

Mesenchymal stem cells, a subpopulation of mesenchymal stromal cells (MSCs), are present in the stroma of several tissues. MSC *in vitro*cultivation for clinical treatments may greatly affect MSC properties. A primary handicap is replicative senescence that impairs MSC functions. Hyaluronan (HA) is present in the extracellular matrix that composes the stem cell niche environment and is under investigation as a key factor for *in vitro* stem cell growth. We evaluated the effect on MSC cultivation of HA hybrid cooperative complexes (HCC) that are obtained from high (H) and low (L) weight molecules (NAHYCO™). We compared this HCC with H-HA and L-HA. We investigated the effects of these HAs on proliferation, cell cycle, apoptosis, senescence, and differentiation following the addition of the polymer solutions in the culture media at concentrations that did not drastically modify the medium

viscosity. Interestingly, 0,16% HCC significantly delayed the senescence compared with the controls. This occurred without alteration of the cell cycle, cytotoxicity, or apoptosis. HCCs also promoted adipogenic and chondrogenic differentiation. Our finding could suggest a potential functional role of HCC above the updated scientific reports of its effects and pave the way to optimization of MSC cultivation for therapeutic application.

Hum Gene Ther. 2018 Jul 11. doi: 10.1089/hum.2018.092. [Epub ahead of print]

Bone Marrow Derived Mesenchymal Stem Cell-Mediated Dual-gene Therapy for Glioblastoma.

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Abstract

Bone marrow mesenchymal stem cells (BMSCs) have been used for systemic delivery of therapeutic genes to solid tumors. However, the optimal treatment time post-BMSCs implantation and the assessment of the long-term fate of therapeutic BMSCs post-tumor treatment are critical if such promising therapies are to be translated into clinical practice. Here, we have developed an efficient BMSCs based therapeutic strategy that simultaneously allows killing of tumor cells, inhibiting of tumor angiogenesis and assessment and eradication of implanted BMSCs after treatment of glioblastoma. BMSCs engineered to co-express the angiogenesis inhibitor kringle 5 (K5) of human plasminogen, under control of the cytomegalovirus promoter (CMV) and the human sodium iodide symporter (NIS), involved in uptake of radioisotopes, under control of Egr1 (early growth response factor 1), a radiation-activated promoter. A significant decrease in tumor growth and tumor angiogenesis and a subsequent increase in survival were observed when mice bearing glioblastoma were treated with 188Re post-therapeutic BMSCs i.v. implantation. Furthermore, the systemic administration of 188Re post-tumor treatment selectively eliminated therapeutic BMSCs expressing NIS, which was monitored in real time by 125I micro-SPECT/CT imaging. Meanwhile, the Egr1 promoter induced a 188Re radiation positive feedback effect absorbed by NIS. After BMSCs i.v. implantation, BMSCs levels in the tumor and lung both peaked on day 10, decreased to the lowest levels on days 24 and 17, respectively. These findings suggest that day 17 post-BMSCs implantation could be an optimal time for 188Re treatment. These results provide a new adjuvant therapy mediated by BMSCs for glioblastoma treatment.

Equine Vet J. 2018 Jul 10. doi: 10.1111/evj.12992. [Epub ahead of print]

Retrospective analysis of local injection site adverse reactions associated with 230 allogenic administrations of bone marrow-derived mesenchymal stem cells in 164 horses.

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Author information

Abstract

BACKGROUND:

Bone marrow derived mesenchymal stem cells (BM-MSCs) are frequently used in the treatment of musculoskeletal injuries. Fully characterised cells that are readily available for use is optimum. Allogenic BM-MSCs can satisfy the need for rapid treatment, however, their safety has been questioned.

OBJECTIVES:

Objectives were to characterise BM-MSCs from an adult donor horse, in vitro, and to identify and describe adverse reactions that occurred following their injection into other horses. We hypothesised that BM-MSCs capable of proliferation, differentiation and lacking MHC II from one donor could be implanted into another individual without significant adverse reactions and the frequency of adverse reactions in clinical cases would be similar to that previously reported for autologous BM-MSCs.

STUDY DESIGN:

Retrospective clinical study.

METHODS:

BM-MSCs were proliferated and characterised from one donor and cryopreserved for clinical use. Medical records for horses injected with allogenic BM-MSCs from this donor at a single hospital were used. After routine lameness exam, lesions were identified using diagnostic ultrasound or MRI. Post injection reaction was defined as increased pain, swelling, or heat at or near injection site, or increased lameness. Treatments required for each reaction were noted.

RESULTS:

BM-MSCs proliferated and underwent differentiation. Cells were found to be negative for MHC-II (<2%) and were viable after cryopreservation and shipping. Ten of 230 (4.35%) injections were noted to be associated with an adverse reaction. Adverse reactions occurred in synovial structures (n = 3) and in soft tissues (n = 7).

MAIN LIMITATIONS:

This investigation could underestimate the number and severity of reactions. Mild reactions, such as synovitis, may have been missed. Also, anti-inflammatory drugs could overshadow mild reactions, making them less likely to be detected.

CONCLUSIONS:

Fully characterised allogenic BM-MSCs originating from a single donor horse can be administered to horses with soft tissue injuries with a low rate of adverse reaction.

Int J Cancer. 2018 Jul 11. doi: 10.1002/ijc.31727. [Epub ahead of print]

Detection of endogenously circulating Mesenchymal Stem Cells in human cancer patients.

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Abstract

Mesenchymal stem cells (MSCs) can play a vital role in tumor progression and anti-cancer therapy response, as demonstrated by various in vitro and in vivo model systems. Their ability to home to developing tumors and modulate the tumor microenvironment, by suppressing T-cell responses and contributing to the tumor stroma, is suggested to have a significant impact on disease progression, metastasis formation and therapy response. Most evidence, however, is derived from artificial models using exogenously administered MSCs. The contribution of endogenous MSCs to tumor progression is currently unclear. Furthermore, few studies have been conducted in humans. A prospective biomarker study was therefore undertaken in 40 human cancer patients and 10 healthy controls of similar age, aimed at (i) exploring and quantifying circulating MSC levels in healthy volunteers and patients with advanced malignancies, (ii) determining the variability of MSC levels between healthy volunteers and cancer patients with different histologic tumor types, and (iii) exploring biomarkers associated with MSC levels. Significantly increased levels of circulating MSC-like cells were observed in cancer patients when compared to healthy individuals (1.72 fold difference, 95% CI 1.03 - 2.81%, p = 0.03). In addition, prior systemic therapy was associated with a significant increase in MSC-like cells (1.73 fold difference, 95% CI 1.02 - 2.95, p = 0.04). These results indicate that the amount of endogenously circulating MSCs in humans is increased in response to cancer, and that systemic anti-cancer treatment can influence MSC levels. Further research is needed to determine whether MSCs have a predictive value.

Adv Clin Exp Med. 2018 Jul 10. doi: 10.17219/acem/70798. [Epub ahead of print]

Safety of adipose-derived cell (stromal vascular fraction - SVF) augmentation for surgical breast reconstruction in cancer patients.

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Abstract

BACKGROUND:

Progress in breast cancer surgery results in a decreased frequency of mastectomy, in the early phases of cancer replaced by breast conserving therapy (lumpectomy). Increased popularity of breast reconstruction by fat or adipose stem cells (ASC)-enriched fat transfer raised uncertainty about the possible risk of increased cancer recurrence. In vitro studies suggest that locally secreted cytokines and reconstructed local blood vessels may stimulate cancer expansion or cancer de novo induction from glandular tissue remaining after lumpectomy.

OBJECTIVES:

The purpose of the study was to evaluate the risk of cancer recurrence in breast cancer patients related to the stromal vascular fraction (SVF) augmentation during autologous fat grafting for breast reconstruction.

MATERIAL AND METHODS:

The tumor recurrence ratio in 56 patients having the breast reconstructed with autologous ASC (transplanted as the subpopulation present in SVF) was compared with the frequency of tumor recurrence in 252 matched patients treated in clinics without subsequent breast reconstruction. Adipose tissue was collected by the Coleman technique and split into 2 portions: one was used for breast reconstruction, the other was enzymatically digested, and isolated cells were used for the augmentation of fat implanted into the breast area. Cancer recurrence in the experimental and matched control group was evaluated following 3-year-long observation time, and the statistical significance of difference in cancer recurrence between the experimental and control group was evaluated.

RESULTS:

Cancer recurrence in the group of patients treated with ASC-enriched fat for breast reconstruction was 3.7% and did not differ significantly from the control group data (4.13%). No adverse effects of therapy were observed.

CONCLUSIONS:

Our study does not produce any data suggesting increased cancer risk following breast reconstruction after a mastectomy or a lumpectomy combined with local radiotherapy. It may be concluded that an autologous transplantation of fat augmented with ASC is a safe and efficient procedure. Longer observation time and the observation of larger numbers of patients would be useful for strengthening the conclusion.

Cell Death Dis. 2018 Jul 9;9(7):754. doi: 10.1038/s41419-018-0791-7.

A novel phosphorylation by AMP-activated kinase regulates RUNX2 from ubiquitination in osteogenesis over adipogenesis.

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Abstract

Mesenchymal stem cells (MSCs) function as progenitors to a variety of cell types. The reported association between osteogenic and adipogenic commitment during differentiation is due to the regulation of key transcription factors in the signaling pathways. However, the process of adipogenesis at the expense of osteogenic phenotype during metabolic stress is still unclear. In this study, we showed for the first time that RUNX2 is a novel substrate of AMP-activated kinase (AMPK), which directly phosphorylates at serine 118 residue in the DNA-binding domain of RUNX2. Our results in in vitro MSC lineage differentiation models confirmed that active AMPK and RUNX2-S118 phosphorylation are preferentially associated with osteogenic commitment, whereas the lack of this phosphorylation leads to adipogenesis. This interplay is regulated by the ubiquitination of non-phosphorylated RUNX2-S118, which is evident in the dominant mutant RUNX2-S118D. Pharmacological activation of AMPK by metformin significantly abrogated the loss of RUNX2-S118

phosphorylation and protected from tunicamycin-induced endoplasmic reticulum stress, high glucose-induced in vitro adipogenesis and streptozotocin-induced in vivo bone adiposity and bone phenotype. In conclusion, results from this study demonstrated that RUNX2 is a direct target of AMPK which simplified the outlook towards several complex mechanisms that are currently established concerning cellular metabolism and pathogenesis.

Knee Surg Relat Res. 2018 Jul 6. doi: 10.5792/ksrr.17.201. [Epub ahead of print]

Intra-Articular Injection of Bone Marrow-Derived Mesenchymal Stem Cells Leading to Better Clinical Outcomes without Difference in MRI Outcomes from Baseline in Patients with Knee Osteoarthritis.

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Author information

Abstract

PURPOSE:

Bone marrow (BM) is frequently used as a source of mesenchymal stem cells (MSCs) because they have a high potential for differentiation. However, it is unclear whether BM-derived MSCs lead to better clinical and magnetic resonance imaging (MRI) outcomes postoperatively.

MATERIALS AND METHODS:

This meta-analysis compared the clinical and MRI outcomes in patients with knee osteoarthritis (OA) treated with BM-derived MSCs. Eight studies comparing the clinical and MRI outcomes assessed with various measurement tools in patients with knee OA treated with BM-derived MSCs were included.

RESULTS:

The range of motion (95% confidence interval [CI], -13.05 to 4.24; p=0.32) and MRI outcomes (95% CI, -0.16 to 1.40; p=0.12) did not differ significantly between the baseline and final follow-up. In contrast, pain (95% CI, 0.89 to 1.87; p＜0.001) and functional outcomes (95% CI, 0.70 to 2.07; p＜0.001) were significantly improved at the final follow-up when compared to the baseline.

CONCLUSIONS:

This meta-analysis found no significant difference in the tested range of motion and MRI outcomes between the baseline and the final follow-up in patients treated with BM-derived MSCs, whereas significant functional improvement and pain relief were noted when compared with the baseline. Thus, BM-derived MSCs appear to be a viable alternative for patients with knee OA, although long-term and high-quality randomized controlled trials are needed to confirm the clinical benefits.

Cell Tissue Res. 2018 Jul 10. doi: 10.1007/s00441-018-2879-x. [Epub ahead of print]

Bone marrow-derived versus adipose-derived stem cells in wound healing: value and route of administration.

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Author information

Abstract

The stem cells with their distinct ability of self-renewal and differentiation are considered an innovation in wound healing. However, there is lack of studies comparing the differential effect of the type and administration route of stem cells in the wound healing context. Thus, the current study has been designed to elucidate the effect of two of the most important stem cell types-the bone marrow-derived and adipose-derived stem cells in full thickness wound healing-and to evaluate, in this optimized wound model, the effectiveness of intradermal versus intravenous routes using H&E, Masson's trichrome, and PKH26-stained sections. It also evaluated the immunohistochemical expression of the stem cell-related surface markers-Ki67, CD71, CD146, CD90, and CD163-and also assessed the level of TNFα and gene expression of NF-κB as two important inflammatory markers. The study revealed that the adipose stem cell groups have shown statistically significant improvement in inflammation, granulation tissue re-organization, and collagen deposition relative to their bone marrow-treated counterparts. The intradermally treated adipose stem cell group, in particular, has demonstrated the most supreme features regarding the expression of the proliferation-related surface markers Ki67 and CD71 as well as in the expression of CD90 in keratinocytes and hair follicle dermal sheaths. The same group has shown the lowest level of TNFα and the best outcome in the parameters of neo-epidermal thickness, granulation tissue re-organization, and pattern of collagen deposition. The systemically treated wounds have displayed superior expression of CD146-positive endothelial cells and dermal fibroblasts as well as better expression of CD163+ macrophages.