Stem cells to restore insulin production and cure diabetes.

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Abstract

BACKGROUND:

The advancement of knowledge in the field of regenerative medicine is increasing the therapeutic expectations of patients and clinicians on cell therapy approaches. Within these, stem cell therapies are often evoked as a possible therapeutic option for diabetes, already ongoing or possible in the near future.

AIM:

The purpose of this document is to make a point of the situation on existing knowledge and therapies with stem cells to treat patients with diabetes by focusing on some of the aspects that most frequently raise curiosity and discussion in clinical practice and in the interaction with the patient. In fact, at present there are no clinically approved treatments based on the use of stem cells for the treatment of diabetes, but several therapeutic approaches have already been evaluated or are being evaluated in clinical trials.

DATA SYNTHESIS:

It is possible to identify three large potential application fields: 1) the reconstruction of the β cell mass; 2) the immunomodulation in type 1 diabetes (T1D); 3) the treatment of complications. In this study we will limit the discussion to approaches that have the potential for clinical translation, deliberately omitting aspects of basic biology and preclinical data. Also, we intentionally omit the treatment of the complications that will be the subject of a future document. Finally, an overview of the Italian situation regarding the storage of cord blood cells for the therapy of diabetes will be given.


The dichotomy of placenta-derived cells in cancer growth.
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Author information

Abstract

Placenta-derived mesenchymal stromal cells (MSC) have often been considered to linger behind their equivalents from other tissues, such as MSC from bone marrow, in many aspects including their therapeutic potential in regenerative medicine. Nowadays however, it is clear that certain aspects make placental MSC attractive as a cellular therapy, such as their lack of ethical concerns and ease of isolation from human term placenta, a material long regarded as biological waste. Moreover, placental MSC virtually lack expression of human leukocyte antigens and co-stimulatory molecules, making them very attractive for transplantation in allogeneic settings. In the context of cancer, cell therapy remains an area of intense investigation whereby MSC have been shown to play opposing roles, and placental MSC are no exception. In this review, we will discuss dichotomy of placental MSC that underscores the challenges in understanding their therapeutic potential in oncology.


The impact of human adipose tissue-derived stem cells on breast cancer cells: implications for cell-assisted lipotransfers in breast reconstruction.

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Author information

Abstract

BACKGROUND:

In this study we evaluated the interactions of human adipose tissue-derived stem cells (ADSCs) and different human breast cancer cell lines (BRCAs) with regard to the safety of cell-assisted lipotransfers for breast reconstruction and a thereby unintended co-localization of ADSCs and BRCAs.

METHODS:

ADSCs were co-cultured with five different human BRCAs (MCF-7, MDA-MB-231, SK-BR-3, ZR-75-30, and EVSA-T) and primary BRCAs from one patient in a transwell system, and cell-cell-interactions were analyzed by assessing doubling time, migration and invasion, angiogenesis, quantitative real-time polymerase chain reaction (PCR) of more than 300 tumor-associated genes, and multiplex protein assays of 20 chemokines and growth factors and eight matrix
metalloproteinases (MMPs). Results of co-culture were compared to those of the respective monoculture.

RESULTS:

Quantitative real-time PCR revealed remarkable changes in the expression of multiple tumor-associated genes in co-culture compared to monocultures of both ADSCs and BRCAs. Concomitantly, the concentration of several tumor-associated proteins, such as cytokines and MMPs, were strongly increased in co-culture. Furthermore, exclusively in co-culture with ADSCs, the different BRCAs were exposed to several important tumor-modulating proteins, such as CCL2, HGF, or interleukins. Co-culture did not significantly affect cellular proliferation of either ADSCs or BRCAs (p > 0.05). The migration of MCF-7 and MDA-MB-231 BRCAs was significantly increased in co-culture with ADSCs by a mean of 11% and 23%, respectively (p = 0.04 and 0.012), as well as that of ADSCs in co-culture with MDA-MB-231, ZR-75-30, and EVSA-T (+11-15%, p = 0.035-0.045). Co-culture with MDA-MB-231, SK-BR-3, and EVSA-T BRCAs significantly increased the invasive behavior of ADSCs by a mean of 24-41% (p = 0.014-0.039). There were no significant differences in the in vitro invasive properties of BRCAs in co-culture compared to monoculture. An in vitro angiogenesis assay revealed an increased tube formation of conditioned media from co-cultured BRCAs and ADSCs compared to the respective monocultures.

CONCLUSION:

This study further elucidates the possible interactions of primary human ADSCs with human BRCAs, pointing towards a potential increased oncological risk which should not be neglected when considering a clinical use of cell-assisted liposarctes in breast reconstruction.


NANOG Plays a Hierarchical Role in the Transcription Network Regulating the Pluripotency and Plasticity of Adipose Tissue-Derived Stem Cells.

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Author information

Abstract

The stromal vascular cell fraction (SVF) of visceral and subcutaneous adipose tissue (VAT and SAT) has increasingly come into focus in stem cell research, since these compartments represent a rich source of multipotent adipose-derived stem cells (ASCs). ASCs exhibit a self-renewal potential and differentiation capacity. Our aim was to study the different expression of the embryonic stem cell markers NANOG (homeobox protein NANOG), SOX2 (SRY (sex determining region Y)-box 2) and OCT4 (octamer-binding transcription factor 4) and to evaluate if there exists a hierarchal role in this network in ASCs derived from both SAT and VAT. ASCs were isolated from SAT and VAT
biopsies of 72 consenting patients (23 men, 47 women; age 45 ± 10; BMI between 25 ± 5 and 30 ± 5 range) undergoing elective open-abdominal surgery. Sphere-forming capability was evaluated by plating cells in low adhesion plastic. Stem cell markers CD90, CD105, CD29, CD31, CD45 and CD146 were analyzed by flow cytometry, and the stem cell transcription factors NANOG, SOX2 and OCT4 were detected by immunoblotting and real-time PCR. NANOG, SOX2 and OCT4 interplay was explored by gene silencing. ASCs from VAT and SAT confirmed their mesenchymal stem cell (MSC) phenotype expressing the specific MSC markers CD90, CD105, NANOG, SOX2 and OCT4. NANOG silencing induced a significant OCT4 (70 ± 0.05%) and SOX2 (75 ± 0.03%) downregulation, whereas SOX2 silencing did not affect NANOG gene expression. Adipose tissue is an important source of MSC, and siRNA experiments endorse a hierarchical role of NANOG in the complex transcription network that regulates pluripotency.


**Early Passage Mesenchymal Stem Cells Display Decreased Radiosensitivity and Increased DNA Repair Activity.**

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**Author information**

**Abstract**

Cell therapies using human mesenchymal stem cells (MSCs) have received much attention in the past decade. In pursuit of the therapeutic potential of MSCs, cell expansion is required to generate a great number of cells with desired phenotype and functionality. Long-term expansion in vitro, however, can lead to altered functions. To explore the changes in DNA damage responses (DDR) in MSCs expanded, DDR pathways following irradiation were characterized in early- and late-passage bone marrow MSCs. Seventy-two hours after irradiation, the percentage of sub-G1 cells in early-passage MSCs did not change significantly. Reduced TUNEL staining was observed in early-passage MSCs compared to late-passage MSCs 4 h after irradiation. Comet assay also revealed that early-passage MSCs were more resistant to irradiation or DNA damages induced by genotoxic agents than late-passage MSCs. ATM phosphorylation and γ-H2AX and phospho-p53 increased in early-passage MSCs while decreased in late-passage MSCs. Through inhibition by KU55933, DDR pathway in early-passage MSCs was shown to be ATM-dependent. Higher levels of poly (ADP-ribose) polymerase-1 (PARP-1) and PAR synthesis were observed in early-passage MSCs than in late-passage MSCs. Knockdown of PARP-1 in early-passage MSCs resulted in sensitization to irradiation-induced apoptosis. Overexpression of PARP-1 in late passage MSCs could render irradiation resistance. Lower activity of DDR in late-passage MSCs was associated with rapid proteasomal degradation of PARP-1. In conclusion, early-passage MSCs are more irradiation-resistant and have increased DDR activity involving PARP-1, ATM and their downstream signals.

Quantitative Assessment of Optimal Bone Marrow Site for the Isolation of Porcine Mesenchymal Stem Cells.

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Author information

Abstract

Background. One of the most plentiful sources for MSCs is the bone marrow; however, it is unknown whether MSC yield differs among different bone marrow sites. In this study, we quantified cellular yield and evaluated resident MSC population from five bone marrow sites in the porcine model. In addition, we assessed the feasibility of a commercially available platelet concentrator (Magellan® MAR01™ Arteriocyte Medical Systems, Hopkinton, MA) as a bedside stem cell concentration device. Methods. Analyses of bone marrow aspirate (BMA) and concentrated bone marrow aspirate (cBMA) included bone marrow volume, platelet and nucleated cell yield, colony-forming unit fibroblast (CFU-F) number, flow cytometry, and assessment of differentiation potential. Results. Following processing, the concentration of platelets and nucleated cells significantly increased but was not significantly different between sites. The iliac crest had significantly less bone marrow volume; however, it yielded significantly more CFUs compared to the other bone marrow sites. Culture-expanded cells from all tested sites expressed high levels of MSC surface markers and demonstrated adipogenic and osteogenic differentiation potential. Conclusions. All anatomical bone marrow sites contained MSCs, but the iliac crest was the most abundant source of MSCs. Additionally, the Magellan can function effectively as a bedside stem cell concentrator


Overexpression of Insulin-Like Growth Factor 1 Enhanced the Osteogenic Capability of Aging Bone Marrow Mesenchymal Stem Cells.

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Author information

Abstract

Many studies have indicated that loss of the osteoblastogenic potential in bone marrow mesenchymal stem cells (bmMSCs) is the major component in the etiology of the aging-related bone deficit. But how the bmMSCs lose osteogenic capability in aging is unclear. Using 2-dimentional cultures, we examined the dose response of human bmMSCs, isolated from adult and aged donors, to exogenous insulin-like growth factor 1 (IGF-1), a growth factor regulating bone
formation. The data showed that the mitogenic activity and the osteoblastogenic potential of bmMSCs in response to IGF-1 were impaired with aging, whereas higher doses of IGF-1 increased the proliferation rate and osteogenic potential of aging bmMSCs. Subsequently, we seeded IGF-1-overexpressing aging bmMSCs into calcium-alginate scaffolds and incubated in a bioreactor with constant perfusion for varying time periods to examine the effect of IGF-1 overexpression to the bone-forming capability of aging bmMSCs. We found that IGF-1 overexpression in aging bmMSCs facilitated the formation of cell clusters in scaffolds, increased the cell survival inside the cell clusters, induced the expression of osteoblast markers, and enhanced the biomineralization of cell clusters. These results indicated that IGF-1 overexpression enhanced cells' osteogenic capability. Thus, our data suggest that the aging-related loss of osteogenic potential in bmMSCs can be attributed in part to the impairment in bmMSCs' IGF-1 signaling, and support possible application of IGF-1-overexpressing autologous bmMSCs in repairing bone defect of the elderly and in producing bone graft materials for repairing large scale bone injury in the elderly.


Engineered cartilage regeneration from adipose tissue derived-mesenchymal stem cells: A morphomolecular study on osteoblast, chondrocyte and apoptosis evaluation.

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Author information

Abstract

The poor self-repair capacity of cartilage tissue in degenerative conditions, such as osteoarthritis (OA), has prompted the development of a variety of therapeutic approaches, such as cellular therapies and tissue engineering based on the use of mesenchymal stem cells (MSCs). The aim of this study is to demonstrate, for the first time, that the chondrocytes differentiated from rat adipose tissue derived-MSCs (AMSCs), are able to constitute a morphologically and biochemically healthy hyaline cartilage after 6 weeks of culture on a Collagen Cell Carrier (CCC) scaffold. In this study we evaluated the expression of some osteoblasts (Runt-related transcription factor 2 (RUNX2) and osteocalcin), chondrocytes (collagen I, II and lubricin) and apoptosis (caspase-3) biomarkers in undifferentiated AMSCs, differentiated AMSCs in chondrocytes cultured in monolayer and AMSCs-derived chondrocytes seeded on CCC scaffolds, by different techniques such as immunohistochemistry, ELISA, Western blot and gene expression analyses. Our results showed the increased expression of collagen II and lubricin in AMSCs-derived chondrocytes cultured on CCC scaffolds, whereas the expression of collagen I, RUNX2, osteocalcin and caspase-3 resulted decreased, when compared to the controls. In conclusion, this innovative basic study could be a possible key for future therapeutic strategies for articular cartilage restoration through the use of CCC scaffolds, to reduce the morbidity from acute cartilage injuries and degenerative joint diseases.