Identification of a Subpopulation of Marrow MSC-Derived Medullary Adipocytes That Express Osteoclast-Regulating Molecules: Marrow Adipocytes Express Osteoclast Mediators.

Holt V, Caplan AI, Haynesworth SE.

Abstract

Increased marrow medullary adipogenesis and an associated decrease in bone mineral density, usually observed in elderly individuals, is a common characteristic in senile osteoporosis. In this study we investigated whether cells of the medullary adipocyte lineage have the potential to directly support the formation of osteoclasts, whose activity in bone leads to bone degradation. An in vitro mesenchymal stem cell (MSC)-derived medullary adipocyte lineage culture model was used to study the expression of the important osteoclast mediators RANKL, M-CSF, SDF-1, and OPG. We further assessed whether adipocytes at a specific developmental stage were capable of supporting osteoclast-like cell formation in culture. In vitro MSC-derived medullary adipocytes showed an mRNA and protein expression profile of M-CSF, RANKL, and OPG that was dependent on its developmental/metabolic stage. Furthermore, RANKL expression was observed in MSC-derived adipocytes that were at a distinct lineage stage and these cells were also capable of supporting osteoclast-like cell formation in co-cultures with peripheral blood mononuclear cells. These results suggest a connection between medullary adipocytes and osteoclast formation in vivo and may have major significance in regards to the mechanisms of decreased bone density in senile osteoporosis.

Osteogenic Potential of Mouse Adipose-Derived Stem Cells Sorted for CD90 and CD105 In Vitro.

Yamamoto M1, Nakata H1, Hao J1, Chou J2, Kasugai S1, Kuroda S1.

Abstract

Adipose tissue-derived stromal cells, termed ASCs, play an important role in regenerative applications. They resemble mesenchymal stem cells owing to their inexhaustibility, general differentiation potential, and plasticity and display a series of cell-specific and cluster-of-differentiation (CD) marker profiles similar to those of other somatic stem cells. Variations in phenotypes or differentiation are intimately associated with CD markers. The purpose of our study was to exhibit distinct populations of ASCs with differing characteristics for osteogenic differentiation. The primary cell batch of murine-derived ASCs was extracted from subcutaneous adipose tissue and the cells were sorted for the expression of the surface protein molecules CD90 and CD105 using flow cytometry. Each cell population sorted for CD90 and CD105 was analyzed for osteogenic potency after cell culture. The results suggested that ASCs exhibit distinct populations with differing characteristics for osteogenic differentiation: unsorted ASCs stimulated comparable mineralized nodule formation as bone marrow stromal cells (BMSCs) in osteogenic medium and viral transfection for BMP2 accelerated the formation of mineralized nodules in CD90 and/or CD105 positive ASCs with observation of decrease in CD105 expression after 14 days. Future studies assessing different immunophenotypes of ASCs should be undertaken to develop cell-based tissue engineering.

Gadolinium-chelate nanoparticle entrapped human mesenchymal stem cell via photochemical internalization for cancer diagnosis.

Kim KS1, Park W1, Na K2.
Abstract

To improve the gadolinium (Gd) internalization efficiency in stem cells, gadolinium-chelate nanoparticles were prepared from a pullulan derivative (pullulan-deoxycholic acid (DOCA)-diethylene triamine pentaacetic (DTPA)-Gd conjugate; PDDG) and then the PDDG was entrapped into human mesenchymal stem cells (hMSCs) by the photochemical-internalization (PCI) method for cancer diagnosis via the cancer homing property of hMSCs. The internalization efficiency of Gd in hMSCs was significantly increased to 98 ± 4 pg Gd/cell from 32 ± 2 pg Gd/cell via the PCI method. Moreover, the Gd-entrapped hMSCs revealed a low exocytosis ratio of gadolinium-chelate nanoparticles during cell division in vitro and a high cellular labeling efficiency for at least 21 days in vivo. The cancer-targeting and diagnosis effect of the Gd-entrapped hMSCs were confirmed in a small CT26 tumor-bearing mice model. The stem cells detected an early tumor (∼3 mm³) within 2 h using 4.7-T MR and optical imaging. The results demonstrated that the PCI-mediated internalization of Gd-incorporated nanoparticles into hMSCs is a promising protocol for efficient cell labeling and tracking.


The Role of Stem Cells in Wound Angiogenesis.

King A1, Balaji S1, Keswani SG1, Crombleholme TM2.

Abstract

Significance: Revascularization plays a critical role in wound healing and is regulated by a complex milieu of growth factors and cytokines. Deficiencies in revascularization contribute to the development of chronic nonhealing wounds. Recent Advances: Stem-cell-based therapy provides a novel strategy to enhance angiogenesis and improve wound healing. With bioethical concerns associated with embryonic stem cells, focus has shifted to different populations of vascular precursors, isolated from adult somatic tissue. Three main populations have been identified: endothelial progenitor cells, mesenchymal stem cells, and induced-pluripotent stem cells. These populations demonstrate great promise to positively influence neovascularization and wound repair. Critical Issues: Further studies to more definitively define each population are necessary to efficiently translate stem-cell-based therapeutic angiogenesis to the bedside. Better understanding of the physiologic pathways of how stem cells contribute to angiogenesis in normal tissue repair will help identify targets for successful therapeutic angiogenesis. Future Directions: Active studies in both animal models and clinical trials are being conducted to develop effective delivery routes, including dosing, route, and timing. Stem-cell-based therapy holds significant potential as a strategy for therapeutic angiogenesis in the care of patients with chronic nonhealing wounds.


Mesenchymal stromal cells from adipose tissue attached to suture material enhance the closure of enterocutaneous fistulas in a rat model.

Volpe BB1, Santos Duarte AD1, Ribeiro TB1, Stocchero I2, Kharmandayan P3, Olalla Saad ST3, Bustoiff-Silva JM4, Malheiros Luzo AC5.

Abstract

BACKGROUND AIMS:

Surgical treatment for enterocutaneous fistulas (EF) frequently fails. Cell therapy may represent a new approach to treatment. Mesenchymal stromal cells (MSCs) have high proliferative and differentiation capacity. This study aimed to investigate whether MSCs could adhere to suture filament (SF), promoting better EF healing.

METHODS:

MSCs, 1 × 10⁶, from adipose tissue (ATMSCs) were adhered to a Polyvicryl SF by adding a specific fibrin glue formulation. Adhesion was confirmed by confocal and scanning electron microscopy (SEM). A cecal
fistula was created in 22 Wistar rats by incising the cecum and suturing the opening to the surgical wound subcutaneously with four separate stitches. The animals were randomly allocated to three groups: control (CG)-five animals, EF performed; injection (IG)-eight animals $1 \times 10^6$ ATMSCs injected around EF borders; and suture filament (SG): nine animals, sutured with $1 \times 10^6$ ATMSCs attached to the filaments with fibrin glue. Fistulas were photographed on the operation day and every 3 days until the 21st day and analyzed by two observers using ImageJ Software.

RESULTS:

Confocal and SEM results demonstrated ATMSCs adhered to SF (ATMSCs-SF). The average reduction size of the fistula area at 21st day was greater for the SG group (90.34%, $P < 0.05$) than the IG (71.80%) and CG (46.54%) groups.

CONCLUSIONS:

ATMSCs adhered to SF maintain viability and proliferative capacity. EF submitted to ATMSCs-SF procedure showed greater recovery and healing. This approach might be a new and effective tool for EF treatment.


A review of therapeutic effects of mesenchymal stem cell secretions and induction of secretory modification by different culture methods.

Madrigal M, Rao KS, Riordan NH.

Abstract

The mesenchymal stem cell (MSC) is being broadly studied in clinical trials. Contrary to the early paradigm of cell replacement and differentiation as a therapeutic mechanism of action, evidence is mounting that the secretions of the cells are responsible for their therapeutic effects. These secretions include molecules and extracellular vesicles that have both local and distant effects. This review summarizes the up- and down-regulation of MSC anti-inflammatory, immune modulating, anti-tumor, and regenerative secretions resulting from different stimuli including: a) hypoxia, which increases the production of growth factors and anti-inflammatory molecules; b) pro-inflammatory stimuli that induce the secretion of immune modulating and anti-inflammatory factors; and c) 3 dimensional growth which up regulates the production of anti-cancer factors and anti-inflammatory molecules compared to monolayer culture. Finally we review in detail the most important factors present in conditioned medium of MSC that can be considered protagonists of MSC physiological effects including HGF, TGF-b, VEGF, TSG-6, PGE2 and galectins 1, and 9. We conclude that there is potential for the development of acellular therapeutic interventions for autoimmune, inflammatory, and malignant diseases and tissue regeneration from cellular secretions derived from MSCs cultured under the appropriate conditions.


To the novel paradigm of proteome-based cell therapy of tumors: through comparative proteome mapping of tumor stem cells and tissue-specific stem cells of humans.

Bryukhovetskiy A, Shevchenko V, Kovalev S, Chekhonin V, Baklaushev V, Bryukhovetskiy I, Zhukova M.

Abstract

We performed proteome mapping, cataloguing and bioinformation analysis of protein lysates of human neural (CD133⁺) progenitor and stem cells (NPSCs) isolated from the olfactory sheath of a nose, multipotent mesenchymal (CD29⁺, CD44⁺, CD73⁺, CD90⁺, CD34⁻) stromal cells (MMSCs) isolated from human bone marrow and tumor (CD133⁺) stem cells (TSCs) isolated from the human U87 glioblastoma cell line. We identified 1664 proteins in the examined lysates of stem cells (SCs), 1052 (63.2%) of which are identical in NPSCs and TSCs and 607 proteins (36.47%) of which are identical in MMSCs and TSCs. Other proteins in
U87 glioblastoma TSCs are oncospecific or carcinogenesis associated. The biological processes, molecular functions, cell localization and protein signal pathways of the proteins available in all three proteomes were annotated by PubMed (http://www.ncbi.nlm.nih.gov/pubmed/), PANTHER (http://www.pantherdb.org/), GeneOntology (http://www.geneontology.org/) and KEGG (http://www.genome.jp/kegg/) databases. It was shown that gliomaspheres of U87 glioblastoma had only 10 intracellular pathways of signal transduction (IPST) that were not modified by the neoplastic process, but only two of them (integrin and focal adhesion pathways) were accessible for regulatory action on gene candidates in the TSC nucleus. Carcinogenesis free membrane proteins, IPST and genes expressing proteins of these pathways in U87 glioblastoma TSCs can be viewed as main targets for regulatory effects on TSCs. We offer a novel concept of proteome-based complex therapy of tumors. This manuscript is published as part of the International Association of Neurorestoratology (IANR) special issue of Cell Transplantation.

Skeletal tissue engineering using mesenchymal or embryonic stem cells: clinical and experimental data.

Gamie Z¹, MacFarlane RJ, Tomkinson A, Moniakis A, Tran GT, Gamie Y, Mantalaris A, Tsiridis E.

Abstract

INTRODUCTION:

Mesenchymal stem cells (MSCs) can be obtained from a wide variety of tissues for bone tissue engineering such as bone marrow, adipose, birth-associated, peripheral blood, periosteum, dental and muscle. MSCs from human fetal bone marrow and embryonic stem cells (ESCs) are also promising cell sources.

AREAS COVERED:

In vitro, in vivo and clinical evidence was collected using MEDLINE® (1950 to January 2014), EMBASE (1980 to January 2014) and Google Scholar (1980 to January 2014) databases.

EXPERT OPINION:

Enhanced results have been found when combining bone marrow-derived mesenchymal stem cells (BMMSCs) with recently developed scaffolds such as glass ceramics and starch-based polymeric scaffolds. Preclinical studies investigating adipose tissue-derived stem cells and umbilical cord tissue-derived stem cells suggest that they are likely to become promising alternatives. Stem cells derived from periosteum and dental tissues such as the periodontal ligament have an osteogenic potential similar to BMMSCs. Stem cells from human fetal bone marrow have demonstrated superior proliferation and osteogenic differentiation than perinatal and postnatal tissues. Despite ethical concerns and potential for teratoma formation, developments have also been made for the use of ESCs in terms of culture and ideal scaffold.


Human umbilical cord mesenchymal stem cells promote carcinoma growth and lymph node metastasis when co-injected with esophageal carcinoma cells in nude mice.


Abstract

BACKGROUND:

Human umbilical cord blood derived-mesenchymal stem cells (hUCMSCs) offer an attractive alternative to bone marrow-derived MSCs (BMMSMCs) for cell-based therapy as it is a less invasive source of biological
material. However, limited studies have been conducted with hUCMSCs as compared to BMMSCs. The present study was conducted to evaluate the effects of hUCMSCs in esophageal carcinoma (EC).

METHODS:

hUCMSCs together with EC cells were transplanted subcutaneously into BALB/c nude mice to observe the effects of hUCMSCs on tumor establishment. hUCMSCs injected through the caudal vein to the mice with pre-established EC to observe the effects of hUCMSCs on tumor outgrowth. In order to elucidate the underlying mechanisms, we also performed in vitro experiments including directly co-culture, transwell assay, proliferation assay and western blotting analysis.

RESULTS:

hUCMSCs promoted EC formation in nude mice. In the in vivo model of pre-established EC, intravenously injected hUCMSCs potently promoted tumor growth. When in vitro co-cultured with hUCMSCs, EC cells proliferation increased. After co-cultured with hUCMSCs through transwell system, EC cells showed increased proliferation. Through transwell assay, we also observed that EC cells recruited MSCs, and MSCs promoted EC cells migration and invasion. Western blotting data showed that the expressions of proliferation related proteins Bcl-2, survivin and metastasis related proteins MMP-2 and MMP-9 were up-regulated in the EC cells transwell co-cultured with hUCMSCs.

CONCLUSIONS:

Our results indicated that hUCMSCs could favor tumor growth in vivo and in vitro. Thus, the exploitation of hUCMSCs in new therapeutic strategies should be cautious under the malignant conditions.


Non-invasive characterization of the adipogenic differentiation of human bone marrow-derived mesenchymal stromal cells by HS-SPME/GC-MS.

Lee DK¹, Yi T², Park KE³, Lee HJ⁴, Cho YK⁵, Lee SJ⁶, Lee J⁷, Park JH⁸, Lee MY⁹, Song SU⁹, Kwon SW¹⁰.

Abstract

A non-invasive method to characterize human mesenchymal stromal cells during adipogenic differentiation was developed for the first time. Seven fatty acid methyl esters (FAMEs), including methyl laurate, methyl myristate, methyl palmitate, methyl linoleate, methyl oleate, methyl elaidate and methyl stearate, were used for characterizing adipogenic differentiation using headspace solid-phase microextraction (HS-SPME) which is a very simple and non-invasive method for the extraction of volatile compounds. Glassware was used for culturing mesenchymal stromal cells rather than the common plasticware to minimize contamination by volatile impurities. The optimal SPME fiber was selected by comparing diverse fibers containing two pure liquid polymers (PDMS and PA) and two porous solids (PDMS/DVB and CAR/PDMS). Using optimized procedures, we discovered that seven FAMEs were only detected in adipogenic differentiated mesenchymal stromal cells and not in the mesenchymal stromal cells before differentiation. These data could support the quality control of clinical mesenchymal stromal cell culture in the pharmaceutical industry in addition to the development of many clinical applications using mesenchymal stromal cells.


Potential use of human adipose mesenchymal stromal cells for intervertebral disc regeneration: a preliminary study on biglycan-deficient murine model of chronic disc degeneration.

Abstract

Introduction

Biglycan is an important proteoglycan of the extracellular matrix of intervertebral disc (IVD), and its decrease with aging has been correlated with IVD degeneration. Biglycan deficient (Bgn ¿/0) mice lack this protein and undergo spontaneous IVD degeneration with aging, thus representing a valuable in vivo model for preliminary studies on therapies for human progressive IVD degeneration. The purpose of the present study was to assess the possible beneficial effects of adipose-derived stromal cells (ADSCs) implants in the Bgn ¿/0 mouse model.

Methods

To evaluate ADSC implant efficacy, Bgn ¿/0 mice were intradiscally (L1-L2) injected with 8x10^4 ADSCs at 16 months old, when mice exhibit severe and complete IVD degeneration, evident at both 7Tesla Magnetic Resonance Imaging (7TMRI) and histology. Placebo and ADSCs treated Bgn ¿/0 mice were assessed by 7TMRI analysis up to 12 weeks post-transplantation. Mice were then sacrificed and implanted discs were analyzed by histology and immunohistochemistry for the presence of human cells and for the expression of biglycan and aggrecan in the IVD area.

Results

After in vivo treatment, 7TMRI revealed evident increase in signal intensity within the discs of mice that received ADSCs, while placebo treatment did not show any variation. Ultrastructural analyses demonstrated that human ADSC survival occurred in the injected discs up to 12 weeks after implant. These cells acquired a positive expression for biglycan, and this proteoglycan was specifically localized in human cells. Moreover, ADSC treatment resulted in a significant increase of aggrecan tissue levels.

Conclusion

Overall, this work demonstrate that ADSC implant into degenerated disc of Bgn ¿/0 mice ameliorates disc damage, promotes new expression of biglycan and increased levels of aggrecan. This suggests a potential benefit of ADSC implant in the treatment of chronic degenerative disc disease and prompts further studies in this field.


Homing of mesenchymal stem cells: mechanistic or stochastic? Implications for targeted delivery in arthritis.

Eseonu OI¹, De Bari C².

Abstract

Mesenchymal stem cells (MSCs) are multipotent cells with the capacity to undergo chondrogenic differentiation. Systemically administered MSCs have been shown to preferentially accumulate at sites of tissue damage and inflammation, thus MSC-based therapy holds great promise for the treatment of inflammatory diseases such as RA. Modulation of MSC homing may allow targeted delivery of systemically administered MSCs to damaged articular cartilage, where they can suppress immune-mediated cartilage destruction and contribute to cartilage repair via a combination of chondrogenic differentiation and paracrine stimulation of intrinsic residual repair. To harness the potential of MSC homing, a thorough understanding of the mechanism is key. This review discusses current knowledge of the mechanism of MSC homing to injured/inflamed tissue and its implications for targeted MSC-based therapy in arthritis.


Intravital Imaging of Mesenchymal Stem Cell Trafficking and Association with Platelets and Neutrophils.

Teo GS¹, Yang Z, Carman CV, Karp JM, Lin CP.

Abstract

Early events of MSC adhesion to and transmigration through the vascular wall following systemic infusion are important for MSC trafficking to inflamed sites, yet are poorly characterized in vivo. Here, we used intravital confocal imaging to determine the acute extravasation kinetics and distribution of culture-expanded MSC (2-6 hours post-infusion) in a murine model of dermal inflammation. By 2 h post-infusion, among the MSC that arrested within the inflamed ear dermis, 47.8±8.2% of MSC had either initiated or completed transmigration into the extravascular space. Arrested and transmigrating MSC were equally distributed within both small capillaries and larger venules. This suggested existence of an active adhesion mechanism, since venule diameters were greater than those of the MSC. Heterotypic intravascular interactions between distinct blood cell types have been reported to facilitate the arrest and extravasation of leukocytes and circulating
tumor cells. We found that 42.8±24.8% of intravascular MSC were in contact with neutrophil-platelet clusters. A role for platelets in MSC trafficking was confirmed by platelet depletion, which significantly reduced the preferential homing of MSC to the inflamed ear, though the total percentage of MSC in contact with neutrophils was maintained. Interestingly, although platelet depletion increased vascular permeability in the inflamed ear, there was decreased MSC accumulation. This suggests that increased vascular permeability is unnecessary for MSC trafficking to inflamed sites. These findings represent the first glimpse into MSC extravasation kinetics and microvascular distribution in vivo, and further clarify the roles of active adhesion, the intravascular cellular environment and vascular permeability in MSC trafficking.


Complete resolution of avascular necrosis of the human femoral head treated with adipose tissue-derived stem cells and platelet-rich plasma.

Pak J1, Lee JH2, Jeon JH3, Lee SH4.

Abstract

We report a case of a 43-year-old man with early stage (stage 1) avascular necrosis (AVN) of the femoral head treated with adipose tissue-derived stem cells (ASCs) and platelet-rich plasma (PRP). ASC-containing stromal vascular fraction was mixed with PRP and hyaluronic acid. This mixture was then injected into the diseased hip under ultrasound guidance. The affected hip was reinjected weekly with additional PRP for 4 weeks. The patient was followed-up with sequential magnetic resonance imaging (MRI) scans at 3, 18, and 21 months after treatment, together with Visual Analogue Scale (VAS) Walking Index, Functional Rating Index, Harris Hip Score, and Range of Motion (ROM) assessments. The patient's severe hip pain was considerably improved at 3 months after treatment, with pain scores, ROM and MRI showing near complete resolution of AVN. Pain scores, ROM and MRI at 18 and 21 months after treatment indicated complete resolution of AVN. This case represents the first evidence of complete resolution of early stage AVN of the hip following treatment with ASCs/PRP.