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The therapeutic potential of human adipose-derived mesenchymal stem cells producing CXCL10 in a mouse melanoma lung metastasis model.

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Author information

Abstract

Interferon γ-induced protein 10 kDa (IP-10) is a potent chemoattractant and has been suggested to enhance antitumor activity and mediate tumor regression through multiple mechanisms of action. Multiple lines of evidence have indicated that genetically-modified adult stem cells represent a potential source for cell-based cancer therapy. In the current study, we assessed therapeutic potential of human adipose derived mesenchymal stem cells (hADSC) genetically-modified to express IP-10 for the treatment of lung metastasis in an immunocompetent mouse model of metastatic melanoma. A Piggybac vector encoding IP-10 was employed to transfect hADSC ex vivo. Expression and bioactivity of the transgenic protein from hADSCs expressing IP-10 were confirmed prior to in vivo studies. Our results indicated that hADSCs expressing IP-10 could inhibit the growth of B16F10 melanoma cells and significantly prolonged survival. Immunohistochemistry analysis, TUNEL assay and western blot analysis indicated that hADSCs expressing IP-10 inhibited tumor cell growth, hindered tumor infiltration of Tregs, restricted angiogenesis and significantly prolonged survival. In conclusion, our results demonstrated that targeting metastatic tumor sites by hADSC expressing IP-10 could reduce melanoma tumor growth and lung metastasis.

Sci Rep. 2018 Jan 10;8(1):312. doi: 10.1038/s41598-017-18862-1.

Human mesenchymal stem cells lose their functional properties after paclitaxel treatment.

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Author information

Abstract

Mesenchymal stem cells (MSCs) are an integral part of the bone marrow niche and aid in the protection, regeneration and proliferation of hematopoietic stem cells after exposure to myelotoxic taxane anti-cancer agents, but the influence of taxane compounds on MSCs themselves remains incompletely understood. Here, we show that bone marrow-derived MSCs are highly sensitive even to low concentrations of the prototypical taxane compound paclitaxel. While MSCs remained metabolically viable, they were strongly impaired regarding both their proliferation and their functional capabilities

after exposure to paclitaxel. Paclitaxel treatment resulted in reduced cell migration, delays in cellular adhesion and significant dose-dependent inhibition of the stem cells' characteristic multi-lineage differentiation potential. Cellular morphology and expression of the defining surface markers remained largely unaltered. Paclitaxel only marginally increased apoptosis in MSCs, but strongly induced premature senescence in these stem cells, thereby explaining the preservation of the metabolic activity of functionally inactivated MSCs. The reported sensitivity of MSC function to paclitaxel treatment may help to explain the severe bone marrow toxicities commonly caused by taxane-based anti-cancer treatments.

Stem Cell Res Ther. 2018 Jan 10;9(1):6. doi: 10.1186/s13287-017-0740-x.

Automated image analysis detects aging in clinical-grade mesenchymal stromal cell cultures.

Oja S[1], Komulainen P[2,3], Penttilä A[2,4], Nystedt J[2], Korhonen M[2,5].
Author information

Abstract

BACKGROUND:

Senescent cells are undesirable in cell therapy products due to reduced therapeutic activity and risk of aberrant cellular effects, and methods for assessing senescence are needed. Early-passage mesenchymal stromal cells (MSCs) are known to be small and spindle-shaped but become enlarged upon cell aging. Indeed, cell morphology is routinely evaluated during MSC production using subjective methods. We have therefore explored the possibility of utilizing automated imaging-based analysis of cell morphology in clinical cell manufacturing.

METHODS:

An imaging system was adopted for analyzing changes in cell morphology of bone marrow-derived MSCs during long-term culture. Cells taken from the cultures at the desired passages were plated at low density for imaging, representing morphological changes observed in the clinical-grade cultures. The manifestations of aging and onset of senescence were monitored by population doubling numbers, expression of $p16^{INK4a}$ and $p21^{Cip1/Waf1}$, β-galactosidase activity, and telomeric terminal restriction fragment analysis.

RESULTS:

Cell area was the most statistically significant and practical parameter for describing morphological changes, correlating with biochemical senescence markers. MSCs from passages 1 (p1) and 3 (p3) were remarkably uniform in size, with cell areas between 1800 and 2500 μm^2. At p5 the cells began to enlarge resulting in a 4.8-fold increase at p6-9 as compared to p1. The expression of $p16^{INK4a}$ and activity of β-galactosidase had a strong correlation with the increase in cell area, whereas the expression of $p21^{Cip1/Waf1}$ reached its maximum at the onset of growth arrest and subsequently decreased. Mean telomere length shortened at an apparently constant rate during culture, from 8.2 ± 0.3 kbp at p1, reaching 6.08 ± 0.6 kbp at senescence.

CONCLUSIONS:

Imaging analysis of cell morphology is a useful tool for evaluating aging in cell cultures throughout the lifespan of MSCs. Our findings suggest that imaging analysis can reproducibly detect aging-related changes in cell morphology in MSC cultures. These findings suggest that cell morphology is still a supreme measure of cell quality and may be utilized to develop new noninvasive imaging-based methods to screen and quantitate aging in clinical-grade cell cultures.

Sci Rep. 2018 Jan 10;8(1):230. doi: 10.1038/s41598-017-18431-6.

Xeno-free pre-vascularized spheroids for therapeutic applications.

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Author information

Abstract

Spheroid culture has gained increasing popularity, arising as a promising tool for regenerative medicine applications. Importantly, spheroids may present advantages over single-cell suspensions in cell-based therapies (CT). Unfortunately, most growth media used for spheroid culture contain animal origin-components, such as fetal bovine serum (FBS). The presence of FBS compromises the safety of CT and presents economic and ethical constraints. SCC (supplement for cell culture) is a novel xeno-free (XF) industrial cell culture supplement, derived from well-controlled pooled human plasma and processed under good manufacturing practice rules. Here, we developed a XF SCC-based formulation for 2D-culture of outgrowth endothelial cells (OEC), and then used it for generating co-culture spheroids of OEC and mesenchymal stem cells (MSC). XF MSC-OEC spheroids were characterized in detail and compared to spheroids cultured in FBS-supplemented medium. XF spheroids presented comparable integrity, size and morphology as the reference culture. The use of both media resulted in spheroids with similar structure, abundant extracellular matrix deposition and specific patterns of OEC distribution and organization. Notably, XF spheroids presented significantly enhanced angiogenic potential, both in vitro (fibrin sprouting assay) and in vivo (CAM assay). These findings are particularly promising in the context of potential therapeutic applications.

Stem Cell Res Ther. 2018 Jan 10;9(1):4. doi: 10.1186/s13287-017-0736-6.

First clinical case report of local microinjection of autologous fat and adipose-derived stromal vascular fraction for perianal fistula in Crohn's disease.

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Author information

Abstract

Mesenchymal stem cell therapy is a promising treatment for perianal Crohn's fistulas refractory to conventional therapy, which are an extremely morbid complication and a true therapeutic challenge.

Autologous adipose-derived stromal vascular fraction (ADSVF) is an easily accessible source of cells with angiogenic, anti-inflammatory, immunomodulatory, and regenerative properties. Here, we describe a case involving a patient with severe perianal Crohn's fistulas refractory to the best medical and surgical practices who received local treatment with ADSVF and microfat. This patient was first examined under anesthesia with drainage via seton placement; 1 week later, on a single day, he underwent adipose tissue extraction, ADSVF and microfat preparation, and the local injection of 14 ml of microfat and approximately 20 million viable ADSVF cells into the soft tissue around the fistulas. No serious adverse events were observed. At the first endpoint at 12 weeks, the fistula had clinically healed with complete re-epithelialization of all external openings; no fistula tract was detected on magnetic resonance imaging, confirming this finding. This good clinical outcome was sustained at 48 weeks and was associated with a reduction in the severity of perianal disease and an improvement in quality of life. The current case highlights the therapeutic potential of a new cellular treatment for Crohn's patients with refractory perianal fistulas based on the innovative hypothesis that the combined action of ADSVF in association with the trophic characteristics of a microfat graft could be beneficial for this condition.

J BUON. 2017 Nov-Dec;22(6):1517-1524.

Genetically engineered bone marrow-derived mesenchymal stem cells co-expressing IFN-γ and IL-10 inhibit hepatocellular carcinoma by modulating MAPK pathway.

Wang H[1], Wang J, Shi X, Ding Y.
Author information

Abstract

PURPOSE:

One of the major challenges in delivering cytokines for the treatment of hepatocellular carcinoma (HCC) is the mode of delivery. This study hypothesized that genetically engineered bone marrow derived mesenchymal stem cells (BMSCs) co-expressing IFN-γ and IL-10 can serve as a potential therapeutic strategy in the treatment of HCC by inhibiting cell proliferation.

METHODS:

Male Sprague-Dawley rats (n=5, 200-250 g) for BMSCs isolation and Nude/SCID mice (n=35,12-20g) to develop liver cancer xenograft model were used. Mice were subcutaneously injected HepG2 cell suspension on left flank. BMSCs were genetically engineered with the recombinant lentiviral vectors expressing IFN-γ and IL-10. The experiments were performed in 5 groups (phosphate buffered saline/PBS, BMSCs, BMSC-IFN-γ, BMSC-IL-10 and BMSC-IFN-γ-IL-10) and the genetically engineered BMSCs were transplanted into HCC mice. Cell viability was measured by MTT assay followed by the evaluation of the effect of cell-cycle regulators (p21, p27, cyclin D1 and Rb). Protein expression of p38, ERK and JNK was assessed by immunohistochemistry using the cell proliferation marker Ki67.

RESULTS:

The combination of two cytokines (IFN-γ and IL- 10) engineered into BMSCs resulted in a significant reduction in HepG2 cell viability (*p<0.05 vs PBS-treated and #p<0.05 vs BMSC-treated group). Significantly increased expression of cell cycle inhibitors p21 and p27 in parallel with reduced cyclin D1 expression were observed. Reduced phosphorylation of Rb demonstrated the repression of G1/S progression. BMSC-IFN-γ-IL-10 treatment significantly reduced the tumor growth at the end of 36 days compared to the group treated with PBS or BMSCs alone. This effect was accompanied with the modulation of MAPK pathway with the activation of p38 and JNK, and inactivation of ERK.

CONCLUSION:

The co-expression of IFN-γ and IL-10 in BMSCs inhibits HCC in vitro and in vivo by modulating cell cycle regulators and MAPK pathway.

Biomaterials. 2018 Jan 2. pii: S0142-9612(17)30834-7. doi: 10.1016/j.biomaterials.2017.12.025. [Epub ahead of print]

Mesenchymal stem cell-macrophage crosstalk and bone healing.

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Author information

Abstract

Recent research has brought about a clear understanding that successful fracture healing is based on carefully coordinated cross-talk between inflammatory and bone forming cells. In particular, the key role that macrophages play in the recruitment and regulation of the differentiation of mesenchymal stem cells (MSCs) during bone regeneration has been brought to focus. Indeed, animal studies have comprehensively demonstrated that fractures do not heal without the direct involvement of macrophages. Yet the exact mechanisms by which macrophages contribute to bone regeneration remain to be elucidated. Macrophage-derived paracrine signaling molecules such as Oncostatin M, Prostaglandin E2 (PGE2), and Bone Morphogenetic Protein-2 (BMP2) have been shown to play critical roles; however the relative importance of inflammatory (M1) and tissue regenerative (M2) macrophages in guiding MSC differentiation along the osteogenic pathway remains poorly understood. In this review, we summarize the current understanding of the interaction of macrophages and MSCs during bone regeneration, with the emphasis on the role of macrophages in regulating bone formation. The potential implications of aging to this cellular cross-talk are reviewed. Emerging treatment options to improve facture healing by utilizing or targeting MSC-macrophage crosstalk are also discussed.

Cell Commun Signal. 2018 Jan 5;16(1):2. doi: 10.1186/s12964-018-0215-4.

Enhanced metastatic capacity of breast cancer cells after interaction and hybrid formation with mesenchymal stroma/stem cells (MSC).

Melzer C[1], von der Ohe J[1], Hass R[2].
Author information

Abstract

BACKGROUND:

Fusion of breast cancer cells with tumor-associated populations of the microenvironment including mesenchymal stroma/stem-like cells (MSC) represents a rare event in cell communication whereby the metastatic capacity of those hybrid cells remains unclear.

METHODS:

Functional changes were investigated in vitro and in vivo following spontaneous fusion and hybrid cell formation between primary human MSC and human MDA-MB-231 breast cancer cells. Thus, lentiviral eGFP-labeled MSC and breast cancer cells labeled with mcherry resulted in dual-fluorescing hybrid cells after co-culture.

RESULTS:

Double FACS sorting and single cell cloning revealed two different aneuploid male hybrid populations (MDA-hyb1 and MDA-hyb2) with different STR profiles, pronounced telomerase activities, and enhanced proliferative capacities as compared to the parental cells. Microarray-based mRNA profiling demonstrated marked regulation of genes involved in epithelial-mesenchymal transition and increased expression of metastasis-associated genes including S100A4. In vivo studies following subcutaneous injection of the breast cancer and the two hybrid populations substantiated the in vitro findings by a significantly elevated tumor growth of the hybrid cells. Moreover, both hybrid populations developed various distant organ metastases in a much shorter period of time than the parental breast cancer cells.

CONCLUSION:

Together, these data demonstrate spontaneous development of new tumor cell populations exhibiting different parental properties after close interaction and subsequent fusion of MSC with breast cancer cells. This formation of tumor hybrids contributes to continuously increasing tumor heterogeneity and elevated metastatic capacities.

Res Vet Sci. 2017 Dec 27;117:246-254. doi: 10.1016/j.rvsc.2017.12.018. [Epub ahead of print]

Equine allogeneic chondrogenic induced mesenchymal stem cells: A GCP target animal safety and biodistribution study.

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Author information

Abstract

The safety of the intra-articular use of mesenchymal stem cells (MSCs) is scarcely reported. Therefore, the goal of this study was to investigate the safety of a single intra-articular injection with allogeneic chondrogenic induced MSCs combined with equine plasma (=the investigational product: IVP) compared to a saline (0.9% NaCl) placebo control (=control product: CP). Sixteen healthy experimental horses were randomly assigned to receive a single intra-articular injection with either the IVP (n=8) or the CP (n=8) in the left metacarpophalangeal joint. All horses underwent a daily clinical assessment

throughout the entire study period of 42days to assess adverse events. Additionally, a local joint assessment and a lameness examination were performed daily during the first two weeks, and weekly the following 4weeks. Blood samples were taken weekly for hematological and biochemical analysis. At the end of the study period, horses of the IVP group were euthanized for a thorough necropsy and to check for biodistribution. Tissue samples of the injected joint were collected for histological examination. In both CP and IVP treated horses a mild transient subjective increase in periarticular temperature and lameness was noted after the intra-articular injection with no significant differences between the treatment groups. No distribution of the cells was found using immunohistochemistry and no ectopic tissue formation or signs of inflammation were found on histology. A single intra-articular injection of allogeneic chondrogenic induced MSCs combined with allogeneic plasma in horses had the same clinical side effects as an intra-articular injection with saline solution.

Advanced 3D models culture to investigate mesenchymal stromal cells of the human dental follicle.

Steimberg N[1], Angiero F[2], Farronato D[3], Berenzi A[4], Cossellu G[5,6], Ottonello A[7], Kaigler D[8], Mazzoleni G[9].
Author information

Abstract

The human dental follicle (hDF) contains the developing tooth and is involved in regulating tooth maturation and eruption. To investigate the mesenchymal stromal cells of the dental follicle, two 3D culture models were used, based on a dynamic bioreactor: the Rotary Cell Culture System (RCCS) and the 3D culture of precursor cells isolated from follicular tissue (hDFCs). The hDFCs were obtained from impacted third molars of 20 patients. Two 3D culture models were tested. In the first model, intact hDF explants were cultured in 3D conditions, preserving the original tissue architecture; they were studied via histomorphological and molecular analyses. The second model involved the 3D culture of hDFCs, which were characterized to evaluate their multipotency in terms of differentiation capability. Of the biomarkers known to characterize hDFCs, hDF precursors were selected for our study. The immunophenotype and in situ immunocytochemistry were evaluated for markers CD44, CD90, CD146, CD105, CD31, CD34 and CD45Ag. The results show that the conditions provided by the RCCS preserve the original organizational architecture of the cells. The 3D conditions of the model enhanced differentiation in response to adipogenic, osteogenic, chondrogenic inductive growth media. The immunophenotype and the immunocytochemistry showed generally high expression of CD90, CD44 and CD105, while CD146 expression was more restricted to approximately 30% of cells. No expression was observed for CD31, CD34 and CD45 Ags.

CONCLUSION:

Two 3D tissue- and cell-based ex vivo models of the hDF supported the long-term maintenance of hDF-specific cell phenotypes and their ability to recapitulate typical cellular differentiation states. As such, these ex vivo models could be used to study the physio-pathology of human odontogenesis.

Additionally, in a therapeutic context, they could be used to examine the role of specific chemical signals (e.g. new therapeutic agents) in the processes of dental tissue repair and regeneration.

Front Immunol. 2017 Dec 18;8:1770. doi: 10.3389/fimmu.2017.01770. eCollection 2017.

Mesenchymal Stromal/Stem Cells: A New Era in the Cell-Based Targeted Gene Therapy of Cancer.

Marofi F[1], Vahedi G[2], Biglari A[3], Esmaeilzadeh A[4,5], Athari SS[4].
Author information

Abstract

In recent years, in light of the promising potentials of mesenchymal stromal/stem cells (MSCs) for carrying therapeutic anticancer genes, a complete revisitation on old chemotherapy-based paradigms has been established. This review attempted to bring forward and introduce the novel therapeutic opportunities of using genetically engineered MSCs. The simplicities and advantages of MSCs for medical applications make them a unique and promising option in the case of cancer therapy. Some of the superiorities of using MSCs as therapeutic gene micro-carriers are the easy cell-extraction procedures and their abundant proliferation capacity *in vitro* without losing their main biological properties. Targeted therapy by using MSCs as the delivery vehicles of therapeutic genes is a new approach in the treatment of various types of cancers. Some of the distinct properties of MSCs, such as tumor-tropism, non-immunogenicity, stimulatory effect on the anti-inflammatory molecules, inhibitory effect on inflammatory responses, non-toxicity against the normal tissues, and easy processes for the clinical use, have formed the basis of attention to MSCs. They can be easily used for the treatment of damaged or injured tissues, regenerative medicine, and immune disorders. This review focused on the drugability of MSCs and their potential for the delivery of candidate anticancer genes. It also briefly reviewed the vectors and methods used for MSC-mediated gene therapy of malignancies. Also, the challenges, limitations, and considerations in using MSCs for gene therapy of cancer and the new methods developed for resolution of these problems are reviewed.

Cytotechnology. 2018 Jan 10. doi: 10.1007/s10616-017-0186-0. [Epub ahead of print]

Optimisation of a potency assay for the assessment of immunomodulative potential of clinical grade multipotent mesenchymal stromal cells.

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Author information

Abstract

Clinical use of multipotent Mesenchymal Stromal Cell (MSC)-based medicinal products requires their production in compliance with Good Manufacturing Practices, thus ensuring that the final drug product meets specifications consistently from batch to batch in terms of cell viability, identity, purity and potency. Potency relates to the efficacy of the medicine in its target clinical indication, so adequate release tests need to be defined and validated as quality controls. Herein we report the design and optimisation of parameters affecting the performance of an in vitro cell-based assay for assessing

immunomodulatory potential of clinical grade MSC for human use, based on their capacity to inhibit proliferation of T lymphocytes under strong polyclonal stimuli. The resulting method was demonstrated to be reproducible and relatively simple to execute. Two case studies using clinical grade MSC are presented as examples to illustrate the applicability of the methodology described in this work.

Acta Biomater. 2018 Jan 6. pii: S1742-7061(18)30002-3. doi: 10.1016/j.actbio.2017.12.043. [Epub ahead of print]

Mesenchymal Stem Cell-Derived Extracellular Matrix Enhances Chondrogenic Phenotype of and Cartilage Formation by Encapsulated Chondrocytes in vitro and in vivo.

Yang Y[1], Lin H[2], Shen H[3], Wang B[2], Lei G[4], Tuan RS[5].
Author information

Abstract

Mesenchymal stem cell derived extracellular matrix (MSC-ECM) is a natural biomaterial with robust bioactivity and good biocompatibility, and has been studied as a scaffold for tissue engineering. In this investigation, we tested the applicability of using decellularized human bone marrow derived MSC-ECM (hBMSC-ECM) as a culture substrate for chondrocyte expansion in vitro, as well as a scaffold for chondrocyte-based cartilage repair. hBMSC-ECM deposited by hBMSCs cultured on tissue culture plastic (TCP) was harvested, and then subjected to a decellularization process to remove hBMSCs. Compared with chondrocytes grown on TCP, chondrocytes seeded onto hBMSC-ECM exhibited significantly increased proliferation rate, and maintained better chondrocytic phenotype than TCP group. After being expanded to the same cell number and placed in high-density micromass cultures, chondrocytes from the ECM group showed better chondrogenic differentiation profile than those from the TCP group. To test cartilage formation ability, composites of hBMSC-ECM impregnated with chondrocytes were subjected to brief trypsin treatment to allow cell-mediated contraction, and folded to form 3-dimensional chondrocyte-impregnated hBMSC-ECM (Cell/ECM constructs). Upon culture in vitro in chondrogenic medium for 21 days, robust cartilage formation was observed in the Cell/ECM constructs. Similarly prepared Cell/ECM constructs were tested in vivo by subcutaneous implantation into SCID mice. Prominent cartilage formation was observed in the implanted Cell/ECM constructs 14 days post-implantation, with higher sGAG deposition compared to controls consisting of chondrocyte cell sheets. Taken together, these findings demonstrate that hBMSC-ECM is a superior culture substrate for chondrocyte expansion and a bioactive matrix potentially applicable for cartilage regeneration in vivo.

STATEMENT OF SIGNIFICANCE:

Current cell-based treatments for focal cartilage defects face challenges, including chondrocyte dedifferentiation, need for xenogenic scaffolds, and suboptimal cartilage formation. We present here a novel technique that utilizes adult stem cell-derived extracellular matrix, as a culture substrate and/or encapsulation scaffold for human adult chondrocytes, for the repair of cartilage defects. Chondrocytes

cultured in stem cell-derived matrix showed higher proliferation, better chondrocytic phenotype, and improved redifferentiation ability upon in vitro culture expansion. Most importantly, 3-dimensional constructs formed from chondrocytes folded within stem cell matrix manifested excellent cartilage formation both in vitro and in vivo. These findings demonstrate the suitability of stem cell-derived extracellular matrix as a culture substrate for chondrocyte expansion as well as a candidate bioactive matrix for cartilage regeneration.

World J Orthop. 2017 Dec 18;8(12):853-860. doi: 10.5312/wjo.v8.i12.853. eCollection 2017 Dec 18.

Update on mesenchymal stem cell therapies for cartilage disorders.

Paschos NK[1], Sennett ML[2].
Author information

Abstract

Cartilage disorders, including focal cartilage lesions, are among the most common clinical problems in orthopedic practice. Left untreated, large focal lesions may result in progression to osteoarthritis, with tremendous impact on the quality of life of affected individuals. Current management strategies have shown only a modest degree of success, while several upcoming interventions signify better outcomes in the future. Among these, stem cell therapies have been suggested as a promising new era for cartilage disorders. Certain characteristics of the stem cells, such as their potential to differentiate but also to support healing made them a fruitful candidate for lesions in cartilage, a tissue with poor healing capacity. The aim of this editorial is to provide an update on the recent advancements in the field of stem cell therapy for the management of focal cartilage defects. Our goal is to present recent basic science advances and to present the potential of the use of stem cells in novel clinical interventions towards enhancement of the treatment armamentarium for cartilage lesions. Furthermore, we highlight some thoughts for the future of cartilage regeneration and repair and to explore future perspectives for the next steps in the field.

Cell Death Differ. 2018 Jan 8. doi: 10.1038/s41418-017-0004-4. [Epub ahead of print]

Basal p53 expression is indispensable for mesenchymal stem cell integrity.

Boregowda SV[1], Krishnappa V[1], Strivelli J[1], Haga CL[1], Booker CN[1], Phinney DG[2].
Author information

Abstract

Marrow-resident mesenchymal stem cells (MSCs) serve as a functional component of the perivascular niche that regulates hematopoiesis. They also represent the main source of bone formed in adult bone marrow, and their bifurcation to osteoblast and adipocyte lineages plays a key role in skeletal homeostasis and aging. Although the tumor suppressor p53 also functions in bone organogenesis, homeostasis, and neoplasia, its role in MSCs remains poorly described. Herein, we examined the normal physiological role of p53 in primary MSCs cultured under physiologic oxygen levels. Using knockout mice and gene silencing we show that p53 inactivation downregulates expression of TWIST2,

which normally restrains cellular differentiation to maintain wild-type MSCs in a multipotent state, depletes mitochondrial reactive oxygen species (ROS) levels, and suppresses ROS generation and PPARG gene and protein induction in response to adipogenic stimuli. Mechanistically, this loss of adipogenic potential skews MSCs toward an osteogenic fate, which is further potentiated by TWIST2 downregulation, resulting in highly augmented osteogenic differentiation. We also show that $p53^{-/-}$ MSCs are defective in supporting hematopoiesis as measured in standard colony assays because of decreased secretion of various cytokines including CXCL12 and CSF1. Lastly, we show that transient exposure of wild-type MSCs to 21% oxygen upregulates p53 protein expression, resulting in increased mitochondrial ROS production and enhanced adipogenic differentiation at the expense of osteogenesis, and that treatment of cells with FGF2 mitigates these effects by inducing TWIST2. Together, these findings indicate that basal p53 levels are necessary to maintain MSC bi-potency, and oxygen-induced increases in p53 expression modulate cell fate and survival decisions. Because of the critical function of basal p53 in MSCs, our findings question the use of p53 null cell lines as MSC surrogates, and also implicate dysfunctional MSC responses in the pathophysiology of p53-related skeletal disorders.

Biomater Res. 2018 Jan 2;22:1. doi: 10.1186/s40824-017-0112-8. eCollection 2018.

Enhanced osteogenic commitment of murine mesenchymal stem cells on graphene oxide substrate.

Kim J[#1], Kim HD[#1], Park J[1], Lee ES[1], Kim E[1], Lee SS[2], Yang JK[1], Lee YS[1], Hwang NS[1,2,3].
Author information

Abstract

BACKGROUND:

Tissue engineering is an interdisciplinary field that attempts to restore or regenerate tissues and organs through biomimetic fabrication of scaffolds with specific functionality. In recent years, graphene oxide (GO) is considered as promising biomaterial due to its nontoxicity, high dispersity, and hydrophilic interaction, and these characteristics are key to stimulating the interactions between substrates and cells.

METHOD:

In this study, GO substrates were fabricated via chemically immobilizing GO at 1.0 mg/ml on glass slides. Furthermore, we examined the osteogenic responses of murine mesenchymal-like stem cells, C3H10T1/2 cells, on GO substrates.

RESULTS:

C3H10T1/2 cells on GO substrates resulted in increased cell surface area, enhanced cellular adhesions, and instigated osteogenic differentiation. Furthermore, priming of C3H10T1/2 cells with chondrocyte-conditioned medium (CM) could further induce a synergistic effect of osteogenesis on GO substrates.

CONCLUSIONS:

All of these data suggest that GO substrate along with CM is suitable for upregulating osteogenic responses of mesenchymal stem cells.

Transl Res. 2017 Dec 15. pii: S1931-5244(17)30330-4. doi: 10.1016/j.trsl.2017.12.003. [Epub ahead of print]

Sphingosine-1-phosphate mediates the therapeutic effects of bone marrow mesenchymal stem cell-derived microvesicles on articular cartilage defect.

Xiang C[1], Yang K[2], Liang Z[2], Wan Y[2], Cheng Y[2], Ma D[2], Zhang H[2], Hou W[2], Fu P[3].
Author information

Abstract

Microvesicles (MVs) are emerging as a new mechanism of intercellular communication by transferring cellular components to target cells, yet their function in disease is just being explored. However, the therapeutic effects of MVs in cartilage injury and degeneration remain unknown. We found MVs contained high levels of sphingosine-1-phosphate (S1P) compared with the original bone marrow mesenchymal stem cells (MSCs). The enrichment of S1P in MVs was mediated by sphingosine kinase 1 (SphK1), but not by sphingosine kinase 2 (SphK2). Co-culture of human chondrocytes with MVs resulted in increased proliferation of chondrocytes in vitro, which was mediated by activation of S1P receptor 1 ($S1PR_1$) expressed on chondrocytes. Meanwhile, MVs inhibited interleukin 1 beta-induced human chondrocytes apoptosis in a dose dependent manner. Furthermore, uptake of MVs by primary cultures of human chondrocytes was mediated by CD44 expressed by MVs. Anti-CD44 antibody significantly reduced the uptake of fluorescent protein-labeled MVs by chondrocytes. Further, blocking S1P by its neutralizing antibody significantly inhibited the therapeutic effects of MVs in vivo. Taken together, MVs showed therapeutic potential for treatment of clinical cartilage injury. This therapeutic potential is due to CD44-mediated uptake of MVs by chondrocytes and the S1P/$S1PR_1$axis-mediated proliferative effects of MVs on chondrocytes.