Stem Cell Rev. 2019 Apr 2. doi: 10.1007/s12015-019-09886-3. [Epub ahead of print]

The Therapeutic Potential of Mesenchymal Stromal Cells in the Treatment of Chemotherapy-Induced Tissue Damage.

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Author information

Abstract

Chemotherapy constitutes one of the key treatment modalities for solid and hematological malignancies. Albeit being an effective treatment, chemotherapy application is often limited by its damage to healthy tissues, and curative treatment options for chemotherapy-related side effects are largely missing. As mesenchymal stromal cells (MSCs) are known to exhibit regenerative capacity mainly by supporting a beneficial microenvironment for tissue repair, MSC-based therapies may attenuate chemotherapy-induced tissue injuries. An increasing number of animal studies shows favorable effects of MSC-based treatments; however, clinical trials for MSC therapies in the context of chemotherapy-related side effects are rare. In this concise review, we summarize the current knowledge of the effects of MSCs on chemotherapy-induced tissue toxicities. Both preclinical and early clinical trials investigating MSC-based treatments for chemotherapy-related side reactions are presented, and mechanistic explanations about the regenerative effects of MSCs in the context of chemotherapy-induced tissue damage are discussed. Furthermore, challenges of MSC-based treatments are outlined that need closer investigations before these multipotent cells can be safely applied to cancer patients. As any pro-tumorigenicity of MSCs needs to be ruled out prior to clinical utilization of these cells for cancer patients, the pro- and anti-tumorigenic activities of MSCs are discussed in detail.

Biochem Biophys Res Commun. 2019 Apr 2. pii: S0006-291X(19)30579-0. doi: 10.1016/j.bbrc.2019.03.178. [Epub ahead of print]

The simultaneous downregulation of TRPM7 and MagT1 in human mesenchymal stem cells in vitro: Effects on growth and osteogenic differentiation.

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Author information

Abstract

The magnesium transporters TRPM7 and MagT1 are overexpressed in osteoblastogenesis. We have shown that silencing either TRPM7 or MagT1 accelerates the osteogenic differentiation of human bone mesenchymal stem cells. Here we demonstrate that the simultaneous downregulation of TRPM7 and MagT1 inhibits cell growth and activates autophagy, which is required in the early phases of

osteoblastogenesis. In TRPM7/MagT1 downregulating cells the expression of two transcription factors required for activating osteogenesis, i.e. RUNX2 and OSTERIX, is induced more than in the controls both in the presence and in the absence of osteogenic stimuli, while COL1A1 is upregulated in co-silencing cells as much as in the controls. This explains why we found no differences in calcium deposition. We conclude that one of the two transporters should be expressed to accelerate osteogenic differentiation.

ACS Appl Mater Interfaces. 2019 Apr 3. doi: 10.1021/acsami.8b22724. [Epub ahead of print]

Mechanical Property of Hydrogel and the Presence of Adipose Stem Cells in Tumor Stroma Affect Spheroid Formation in 3D Osteosarcoma Model.

Kundu B, Bastos AR, Brancato V, Cerqueira MT, Oliveira JM, Correlo VM, Reis RL, Kundu SC.

Abstract

Osteosarcoma is one of the most common metastatic bone cancers, results in significant morbidity and mortality. Unfolding of effectual therapeutic strategies against osteosarcoma is impeded due to the absence of adequate animal models, which can truly recapitulate disease biology of humans. Tissue engineering provides an opportunity to develop physiologically relevant, reproducible, tunable in vitro platforms to investigate the interactions of osteosarcoma cells with its microenvironment. Adipose derived stem cells (ASCs) are detected adjacent to osteosarcoma masses; considered to have protumor effects. Hence, the present study focuses on investigating the role of reactive ASCs in formation of spheroids of osteosarcoma cells (Saos 2) within a three-dimensional (3D) niche, which is created using gellan gum - silk fibroin. By modifying the blending ratio of gellan gum - silk, the optimum stiffness of the resultant hydrogels such as GG and GG75: S25 is obtained for cancer spheroid formation. This work indicates that the co-existence of cancer and stem cells can able to form spheroid, the hallmark of cancer, only in a particular micro-environment stiffness. The incorporation of fibrillar silk fibroin within the hydrophilic network of gellan gum in GG75: S25 spongy-like hydrogels closely mimics the stiffness of commercially established cancer biomaterials (e.g. Matrigel, HyStem). The GG75: S25 hydrogel maintains the metabolically active construct for longer time with elevated expression of OPN, OCN, RUNX 2 and BSP genes, the biomarkers of osteosarcoma, compared to GG. The GG75: S25 construct also exhibits intense alkaline phosphatase expression in immunohistochemistry compared to GG, indicating the potentiality of it to serve as biomimetic niche to model osteosarcoma. Taken together, the gellan gum - silk fibroin blended spongy-like hydrogel is envisioned as an alternative low-cost platform for 3D cancer modeling.

Stem Cell Rev. 2019 Apr 6. doi: 10.1007/s12015-019-09883-6. [Epub ahead of print]

Involvement of P2X7 Receptors in the Osteogenic Differentiation of Mesenchymal Stromal/Stem Cells Derived from Human Subcutaneous Adipose Tissue.

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Abstract

The ionotropic P2X7 receptor (P2X7R) is involved in bone homeostasis but its role in osteogenesis is controversial. Thus, we investigated the expression of P2X7R and the effects exerted by its modulation in mesenchymal stromal cells from human subcutaneous adipose tissue (S-ASCs), which have potential therapeutic application in bone regenerative medicine. We found that undifferentiated S-ASCs expressed P2X7R and its functional splice variants P2X7AR and P2X7BR. Cell stimulation by P2X7R agonist BzATP (100 μM) neither modified proliferation nor caused membrane pore opening while increasing intracellular Ca^{2+} levels and migration. The P2X7R antagonist A438079 reversed these effects. However, 25-100 μM BzATP, administered to S-ASCs undergoing osteogenic differentiation, dose-dependently decreased extracellular matrix mineralization and expression of osteogenic transcription factors Runx2, alkaline phosphatase and osteopontin. These effects were not coupled to cell proliferation reduction or to cell death increase, but were associated to decrease in P2X7AR and P2X7BR expression. In contrast, expression of P2X7R, especially P2X7BR isoform, significantly increased during the osteogenic process. Noteworthy, the antagonist A438079, administered alone, at first restrained cell differentiation, enhancing it later. Accordingly, A438079 reversed BzATP effects only in the second phase of S-ASCs osteogenic differentiation. Apyrase, a diphosphohydrolase converting ATP/ADP into AMP, showed a similar behavior. Altogether, findings related to A438079 or apyrase effects suggest an earlier and prevailing pro-osteogenic activity by endogenous ATP and a later one by adenosine derived from endogenous ATP metabolism. Conversely, P2X7R pharmacological stimulation by BzATP, mimicking the effects of high ATP levels occurring during tissue injuries, depressed receptor expression/activity impairing MSC osteogenic differentiation.

Cytokine Growth Factor Rev. 2019 Apr 2. pii: S1359-6101(19)30024-3. doi: 10.1016/j.cytogfr.2019.04.002. [Epub ahead of print]

The mesenchymal stem cell secretome: A new paradigm towards cell-free therapeutic mode in regenerative medicine.

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Author information
Abstract

Mesenchymal Stem Cells (MSCs) have been shown to be a promising candidate for cell-based therapy. The therapeutic potential of MSCs, towards tissue repair and wound healing is essentially based on their paracrine effects. Numerous pre-clinical and clinical studies of MSCs have yielded encouraging results. Further, these cells have been shown to be relatively safe for clinical applications. MSCs harvested from numerous anatomical locations including the bone marrow, adipose tissue, Wharton's jelly of the umbilical cord etc., display similar immunophenotypic profiles. However, there is a large body of evidence showing that MSCs secrete a variety of biologically active molecules such as growth

factors, chemokines, and cytokines. Despite the similarity in their immunophenotype, the secretome of MSCs appears to vary significantly, depending on the age of the host and niches where the cells reside. Thus, by implication, proteomics-based profiling suggests that the therapeutic potential of the different MSC populations must also be different. Analysis of the secretome points to its influence on varied biological processes such as angiogenesis, neurogenesis, tissue repair, immunomodulation, wound healing, anti-fibrotic and anti-tumour for tissue maintenance and regeneration. Though MSC based therapy has been shown to be relatively safe, from a clinical standpoint, the use of cell-free infusions can altogether circumvent the administration of viable cells for therapy. Understanding the secretome of in vitro cultured MSC populations, by the analysis of the corresponding conditioned medium, will enable us to evaluate its utility as a new therapeutic option. This review will focus on the accumulating evidence that points to the therapeutic potential of the conditioned medium, both from pre-clinical and clinical studies. Finally, this review will emphasize the importance of profiling the conditioned medium for assessing its potential for cell-free therapy therapy.

World J Stem Cells. 2019 Mar 26;11(3):180-195. doi: 10.4252/wjsc.v11.i3.180.

Circulating factors present in the sera of naturally skinny people may influence cell commitment and adipocyte differentiation of mesenchymal stromal cells.

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Abstract

BACKGROUND:

Research on physiopathology of obesity may receive new hints from studies on skinny people (SP). These are individuals who show a poor or null gaining of body weight, in spite of high-calorie intake, by far exceeding the body requirements.

AIM:

To evaluate how circulating factors present in the SP sera may affect adipogenesis of mesenchymal stromal cells (MSCs).

METHODS:

We isolated MSCs from bone marrow of healthy donors with both normal body mass index (BMI) and caloric consumption. MSC cultures were primed with sera collected from SP or normal people (NP). Then biomolecular assays were performed to evaluate effect on proliferation, apoptosis, senescence, cell commitment, and differentiation.

RESULTS:

SP priming affected adipocyte cell commitment and reduced spontaneous adipogenesis. Moreover, an in-depth analysis of exogenous-induced adipocyte differentiation showed striking differences between differentiation in SP-primed samples compared with NP ones. In adipocytes from SP cultures we

observed a reduced size of lipid droplets, an increased expression of adipose triglyceride lipase, along with high mitochondria content and ability to produce ATP in starvation condition. These data and the expression of UCP1 protein, indicated that SP pretreatment produced a bias toward brown adipocyte differentiation.

CONCLUSION:
Our data suggest that sera from SP may promote brown adipogenesis rather that white adipocyte differentiation. This finding could explain why SP present normal body composition in spite of an excess of caloric intake. We hypothesize that some circulating components present in the blood of these individuals may favor brown adipogenesis at expense of white adipocyte production.

Bone. 2019 Apr 1. pii: S8756-3282(19)30128-0. doi: 10.1016/j.bone.2019.03.041. [Epub ahead of print]

Aging and lineage allocation changes of bone marrow skeletal (stromal) stem cells.

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Abstract

Aging is associated with decreased bone mass and accumulation of bone marrow adipocytes. Both bone forming osteoblastic cells and bone marrow adipocytes are derived from a stem cell population within the bone marrow stroma called bone marrow stromal (skeletal or mesenchymal) stem cells (BMSC). In the present review, we provide an overview, based on the current literature, regarding the physiological aging processes that cause changes in BMSC lineage allocation, enhancement of adipocyte and defective osteoblast differentiation, leading to gradual exhaustion of stem cell regenerative potential and defects in bone tissue homeostasis and metabolism. We discuss strategies to preserve the "youthful" state of BMSC, to reduce bone marrow age-associated adiposity, and to counteract the overall negative effects of aging on bone tissues with the aim of decreasing bone fragility and risk of fractures.

Biores Open Access. 2019 Mar 29;8(1):32-44. doi: 10.1089/biores.2019.0001. eCollection 2019.

Electroporation: A Sustainable and Cell Biology Preserving Cell Labeling Method for Adipogenous Mesenchymal Stem Cells.

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Author information

Abstract

Human mesenchymal stem cells derived from adipose tissue (AD-hMSCs) represent a promising source for tissue engineering and are already widely used in cell therapeutic clinical trials. Until today, an efficient and sustainable cell labeling system for cell tracking does not exist. We evaluated transient transfection through electroporation for cell labeling and compared it with lentiviral transduction for AD-hMSCs. In addition, we tested whether nonsense DNA or a reporter gene such as enhanced green

fluorescent protein (EGFP) is the more suitable label for AD-hMSCs. Using electroporation, the transfection efficiency reached a maximal level of 44.6 ± 1.1% EGFP-positive cells after selective and expansive cultivation of the mixed MSC population, and was 44.5 ± 1.4% after gene transfer with Cyanin3-marked nonsense-label DNA, which remained stable during 2 weeks of nonselective cultivation (37.2 ± 4.7% positive AD-hMSCs). Electroporation with both nonsense DNA and pEGFP-N1 led to a slight growth retardation of 45.2% and 59.1%, respectively. EGFP-transfected or transduced AD-hMSCs showed a limited adipogenic and osteogenic differentiation capacity, whereas it was almost unaffected in cells electroporated with the nonsense-label DNA. The nonsense DNA was detectable through quantitative real-time polymerase chain reaction for at least 5 weeks/10 passages and in differentiated AD-hMSCs. EGFP-labeled cells were trackable for 24 h *in vitro* and served as testing cells with new materials for dental implants for 7 days. In contrast, lentivirally transduced AD-hMSCs showed an altered natural immune phenotype of the AD-hMSCs with lowered expression of two cell type defining surface markers (CD44 and CD73) and a relevantly decreased cell growth by 71.8% as assessed by the number of colony-forming units. We suggest electroporation with nonsense DNA as an efficient and long-lasting labeling method for AD-hMSCs with the comparably lowest negative impact on the phenotype or the differentiation capacity of the cells, which may, therefore, be suitable for tissue engineering. In contrast, EGFP transfection by electroporation is efficient but may be more suitable for cell tracking within cell therapies without MSC differentiation procedures. Since current protocols of lentiviral gene transduction include the risk of cell biological alterations, electroporation seems advantageous and sustainable enough for hMSC labeling.

PLoS One. 2019 Apr 3;14(4):e0213452. doi: 10.1371/journal.pone.0213452. eCollection 2019.

Emergent heterogeneity in putative mesenchymal stem cell colonies: Single-cell time lapsed analysis.

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Author information

Abstract

Bone marrow stromal cells (BMSCs) include a subset of stem cells that are considered promising for developmental studies and therapeutic applications. While it is appreciated generally that BMSC populations can exhibit morphological and functional heterogeneity upon in vitro culture expansion, the potential for heterogeneity within a single colony forming unit-generated ostensibly from a single mother cell-is less explored but is critical to design of both fundamental studies and cell therapy production. Here we observed BMSC colony formation in real time via time lapsed optical imaging and analysis, to quantify whether and how heterogeneity emerged over multiple cell divisions spanning the duration of a typical colony formation unit assay. These analyses demonstrate that such colonies are neither homogeneous subpopulations of stem cells nor necessarily derived from single originating cells. While the mechanisms for and causes of this intracolony heterogeneity are not understood fully, we further demonstrate that extensive cell-cell contacts do not correlate with senescence, but that media exchange was concurrent with diversification in even the most uniform single-cell-derived colonies.

These direct quantitative observations and visualizations of colony formation provide new insights that are motivated by significant implications for both basic research and stem cell-based therapies.

- **Format**: Abstract

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A cancellous bone matrix system with specific mineralisation degrees for mesenchymal stem cell differentiation and bone regeneration.

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Author information

Abstract

Bone regenerative therapies have been explored using various biomaterial systems. Notably, collagen biomineralisation is believed to be essential for promoting bone regeneration. However, ideal bone repair materials with an appropriate mineralised matrix, superior osteogenic activity with early vascularisation, and recellularisation properties are still needed. This study aimed to develop a method to subject the decellularised cancellous bone matrix (DCBM) to ultrasound to obtain specific demineralisation to investigate the effects of DCBM with different degrees of mineralisation on proliferation and osteogenic differentiation in bone marrow-derived mesenchymal stem cells (BMSCs) and in repairing femoral bone defects in rabbits. We established an optimised native DCBM mineralisation ECM scaffold for bone regeneration. Upon complete decellularisation of the cancellous bone matrix, DCBMs with specific degrees of mineralisation were obtained. We comprehensively evaluated their bioactive components, minimal immunogenicity, ultra-micro-structural mechanical properties, and degree of mineralisation. Furthermore, specific mineralised DCBMs (obtained by low-temperature rapid ultrasound for 4 and 8 h) had prominent effects in promoting the osteogenic differentiation of BMSCs in vitro. Moreover, more newly formed trabeculae, vessels, and endochondral bone were also detected in the aforementioned groups during early-stage bone repair in vivo. The underlying mechanism might be mineralisation-related regulation and ultra-micro-structural mechanical properties. Thus, the present study shows that specific demineralised DCBM obtained under optimal conditions had superior properties to those of unmineralised or completely demineralised DCBM by promoting MSC osteogenic differentiation and initiating endochondral bone formation and de novo osteogenesis.

Bone Joint J. 2019 Apr;101-B(4):361-364. doi: 10.1302/0301-620X.101B4.BJJ-2019-0013.R1.

Cell therapy in orthopaedics: where are we in 2019?

Rodeo SA[1].

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Abstract

Stem cells are defined by their potential for self-renewal and the ability to differentiate into numerous cell types, including cartilage and bone cells. Although basic laboratory studies demonstrate that cell therapies have strong potential for improvement in tissue healing and regeneration, there is little evidence in the scientific literature for many of the available cell formulations that are currently offered to patients. Numerous commercial entities and 'regenerative medicine centres' have aggressively marketed unproven cell therapies for a wide range of medical conditions, leading to sometimes indiscriminate use of these treatments, which has added to the confusion and unpredictable outcomes. The significant variability and heterogeneity in cell formulations between different individuals makes it difficult to draw conclusions about efficacy. The 'minimally manipulated' preparations derived from bone marrow and adipose tissue that are currently used differ substantially from cells that are processed and prepared under defined laboratory protocols. The term 'stem cells' should be reserved for laboratory-purified, culture-expanded cells. The number of cells in uncultured preparations that meet these defined criteria is estimated to be approximately one in 10 000 to 20 000 (0.005% to 0.01%) in native bone marrow and 1 in 2000 in adipose tissue. It is clear that more refined definitions of stem cells are required, as the lumping together of widely diverse progenitor cell types under the umbrella term 'mesenchymal stem cells' has created confusion among scientists, clinicians, regulators, and our patients. Validated methods need to be developed to measure and characterize the 'critical quality attributes' and biological activity of a specific cell formulation. It is certain that 'one size does not fit all' - different cell formulations, dosing schedules, and culturing parameters will likely be required based on the tissue being treated and the desired biological target. As an alternative to the use of exogenous cells, in the future we may be able to stimulate the intrinsic vascular stem cell niche that is known to exist in many tissues. The tremendous potential of cell therapy will only be realized with further basic, translational, and clinical research