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Employing mesenchymal stem cells to support tumor-targeted delivery of extracellular vesicle (EV)-encapsulated microRNA-379.

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Abstract

Adult Mesenchymal Stem Cells (MSCs) have a well-established tumor-homing capacity, highlighting potential as tumor-targeted delivery vehicles. MSCs secrete extracellular vesicle (EV)-encapsulated microRNAs, which play a role in intercellular communication. The aim of this study was to characterize a potential tumor suppressor microRNA, miR-379, and engineer MSCs to secrete EVs enriched with miR-379 for in vivo therapy of breast cancer. miR-379 expression was significantly reduced in lymph node metastases compared to primary tumor tissue from the same patients. A significant reduction in the rate of tumor formation and growth in vivo was observed in T47D breast cancer cells stably expressing miR-379. In more aggressive HER2-amplified HCC-1954 cells, HCC-379 and HCC-NTC tumor growth rate in vivo was similar, but increased tumor necrosis was observed in HCC-379 tumors. In response to elevated miR-379, COX-2 mRNA and protein was also significantly reduced in vitro and in vivo. MSCs were successfully engineered to secrete EVs enriched with miR-379, with the majority found to be of the appropriate size and morphology of exosomal EVs. Administration of MSC-379 or MSC-NTC cells, or EVs derived from either cell population, resulted in no adverse effects in vivo. While MSC-379 cells did not impact tumor growth, systemic administration of cell-free EVs enriched with miR-379 was demonstrated to have a therapeutic effect. The data presented support miR-379 as a potent tumor suppressor in breast cancer, mediated in part through regulation of COX-2. Exploiting the tumor-homing capacity of MSCs while engineering the cells to secrete EVs enriched with miR-379 holds exciting potential as an innovative therapy for metastatic breast cancer.

Indian J Clin Biochem. 2018 Jan;33(1):46-52. doi: 10.1007/s12291-017-0641-x. Epub 2017 Feb 10.

Characterization and Classification of Mesenchymal Stem Cells in Several Species Using Surface Markers for Cell Therapy Purposes.

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Abstract

Mesenchymal stem cells are multipotent cells capable of replicating as undifferentiated cells, and have the potential of differentiating into mesenchymal tissue lineages such as osteocytes, adipocytes and

chondrocytes. Such lineages can then be used in cell therapy. The aim of present study was to characterize bone marrow derived mesenchymal stem cells in four different species, including: sheep, goat, human and mouse. Human bone-marrow mesenchymal stem cells were purchased, those of sheep and goat were isolated from fetal bone marrow, and those of mouse were collected by washing bone cavity of femur and tibia with DMEM/F12. Using flow-cytometry, they were characterized by CD surface antigens. Furthermore, cells of third passage were examined for their osteogenic and adipogenic differentiation potential by oil red and alizarin red staining respectively. According to the results, CD markers studied in the four groups of mesenchymal stem cells showed a different expression. Goat and sheep expressed CD44 and CD166, and weakly expressed CD34, CD45, CD105 and CD90. Similarly, human and mouse mesenchymal cells expressed CD44, CD166, CD105 and CD90 whereas the expression of CD34 and CD45 was negative. In conclusion, although all mesenchymal stem cells display plastic adherence and tri-lineage differentiation, not all express the same panel of surface antigens described for human mesenchymal stem cells. Additional panel of CD markers are necessary to characterize regenerative potential and possible application of these stem cells in regenerative medicine and implantology. Bone. 2018 Jan 20. pii: S8756-3282(18)30023-1. doi: 10.1016/j.bone.2018.01.023. [Epub ahead of print]

Development of a 3D bone marrow adipose tissue model.

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Abstract

Over the past twenty years, evidence has accumulated that biochemically and spatially defined networks of extracellular matrix, cellular components, and interactions dictate cellular differentiation, proliferation, and function in a variety of tissue and diseases. Modeling in vivo systems in vitro has been undeniably necessary, but when simplified 2D conditions rather than 3D in vitro models are used, the reliability and usefulness of the data derived from these models decreases. Thus, there is a pressing need to develop and validate reliable in vitro models to reproduce specific tissue-like structures and mimic functions and responses of cells in a more realistic manner for both drug screening/disease modeling and tissue regeneration applications. In adipose biology and cancer research, these models serve as physiologically relevant 3D platforms to bridge the divide between 2D cultures and in vivo models, bringing about more reliable and translationally useful data to accelerate benchtop to bedside research. Currently, no model has been developed for bone marrow adipose tissue (BMAT), a novel adipose depot that has previously been overlooked as "filler tissue" but has more recently been recognized as endocrine-signaling and systemically relevant. Herein we describe the development of the first 3D, BMAT model derived from either human or mouse bone marrow (BM) mesenchymal stromal cells (MSCs). We found that BMAT models can be stably cultured for at least 3 months in vitro, and that myeloma cells (5TGM1, OPM2 and MM1S cells) can be cultured on these for at least 2 weeks. Upon tumor cell co-culture, delipidation occurred in BMAT adipocytes, suggesting a bidirectional relationship between these two important cell types in the malignant BM niche. Overall, our studies suggest that 3D BMAT represents a "healthier," more realistic tissue model that may be useful for

elucidating the effects of MAT on tumor cells, and tumor cells on MAT, to identify novel therapeutic targets. In addition, proteomic characterization as well as microarray data (expression of >22,000 genes) coupled with KEGG pathway analysis and gene set expression analysis (GSEA) supported our development of less-inflammatory 3D BMAT compared to 2D culture. In sum, we developed the first 3D, tissue-engineered bone marrow adipose tissue model, which is a versatile, novel model that can be used to study numerous diseases and biological processes involved with the bone marrow.

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Tissue-Engineered Bone Immobilized with Human Adipose Stem Cells-Derived Exosomes Promotes Bone Regeneration.

Li W, Liu Y, Zhang P, Tang Y, Zhou M, Jiang W, Zhang X, Wu G, Zhou Y.

Abstract

Exosomes, nano-scale extracellular vesicles (EVs) functioning as cell-to-cell communicator, are emerging promising therapeutics in the field of bone tissue engineering. Here, we report the construct and evaluation of a novel cell-free tissue-engineered bone (TEB) that successfully accelerated the restoration of critical-sized mouse calvarial defects through combining exosomes derived from human adipose-derived stem cells (hASCs) with PLGA scaffolds. The exosomes were immobilized on the polydopamine-coating PLGA (PLGA/pDA) scaffolds under mild chemical conditions. Specifically, we investigated the effects of hASCs-derived exosomes on the osteogenic, proliferation and migration capabilities of human bone marrow-derived stem cells (hBMSCs) in vitro and optimized their osteoinductive effects through osteogenic induction. Furthermore, in vitro assay showed exosomes could release from PLGA/pDA scaffold slowly and consistently, and in vivo results showed this cell-free system enhanced bone regeneration significantly, at least partially through its osteoinductive effects and capacities of promoting mesenchymal stem cells migration and homing in the newly-formed bone tissue. Therefore, overall results demonstrated that our novel cell-free system comprised of hASCs-derived exosomes and PLGA/pDA scaffold provides a new therapeutic paradigm for bone tissue engineering and showed promising potential in repairing bone defects.

Stem Cell Investig. 2017 Dec 19;4:98. doi: 10.21037/sci.2017.12.03. eCollection 2017.

Extracellular vesicles and aging.

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Abstract

Aging and the chronic diseases associated with aging place a tremendous burden on our healthcare system. As our world population ages dramatically over the next decades, this will only increase. Hence, there is a great need to discover fundamental mechanisms of aging to enable development of strategies for minimizing the impact of aging on our health and economy. There is general agreement that cell autonomous mechanisms contribute to aging. As cells accrue damage over time, they respond to it by triggering individual cell fate decisions that ultimately disrupt tissue homeostasis and thus

increase risk of morbidity. However, there are numerous lines of evidence, including heterochronic parabiosis and plasma transfer, indicating that cell non-autonomous mechanisms are critically important for aging as well. In addition, senescent cells, which accumulate in tissues with age, can display a senescence-associated secretory phenotype (SASP) that contributes to driving aging and loss of tissue homeostasis through a non-cell autonomous mechanism(s). Given the diverse roles of blood-borne extracellular vesicles (EVs) in modulating not only the immune response, but also angiogenesis and tissue regeneration, they likely play a key role in modulating the aging process through cell non-autonomous mechanisms. The fact that senescent cells release more EVs and with a different composition suggests they contribute to the adverse effects of senescence on aging. In addition, the ability of EVs from functional progenitor cells to promote tissue regeneration suggests that stem cell-derived EVs could be used therapeutically to extend healthspan. This review focuses on the potential roles of EVs in aging, the potential of EV-based therapeutic applications for extending healthspan and the potential for use of circulating EVs as biomarkers of unhealthy aging.

Stem Cells Int. 2017;2017:1732094. doi: 10.1155/2017/1732094. Epub 2017 Nov 16.

Allogeneic Umbilical Cord-Derived Mesenchymal Stem Cells as a Potential Source for Cartilage and Bone Regeneration: An In Vitro Study.

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Abstract

Umbilical cord (UC) may represent an attractive cell source for allogeneic mesenchymal stem cell (MSC) therapy. The aim of this *in vitro*study is to investigate the chondrogenic and osteogenic potential of UC-MSCs grown onto tridimensional scaffolds, to identify a possible clinical relevance for an allogeneic use in cartilage and bone reconstructive surgery. Chondrogenic differentiation on scaffolds was confirmed at 4 weeks by the expression of sox-9 and type II collagen; low oxygen tension improved the expression of these chondrogenic markers. A similar trend was observed in pellet culture in terms of matrix (proteoglycan) production. Osteogenic differentiation on bone-graft-substitute was also confirmed after 30 days of culture by the expression of osteocalcin and RunX-2. Cells grown in the hypertrophic medium showed at 5 weeks safranin o-positive stain and an increased CbFa1 expression, confirming the ability of these cells to undergo hypertrophy. These results suggest that the UC-MSCs isolated from minced umbilical cords may represent a valuable allogeneic cell population, which might have a potential for orthopaedic tissue engineering such as the on-demand cell delivery using chondrogenic, osteogenic, and endochondral scaffold. This study may have a clinical relevance as a future hypothetical option for allogeneic single-stage cartilage repair and bone regeneration.

J Biosci. 2017 Sep;42(3):373-382.

Differential reduction of reactive oxygen species by human tissuespecific mesenchymal stem cells from different donors under oxidative stress.

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Abstract

Clinical trials using human Mesenchymal Stem Cells (MSCs) have shown promising results in the treatment of various diseases. Different tissue sources, such as bone marrow, adipose tissue, dental pulp and umbilical cord, are being routinely used in regenerative medicine. MSCs are known to reduce increased oxidative stress levels in pathophysiological conditions. Differences in the ability of MSCs from different donors and tissues to ameliorate oxidative damage have not been reported yet. In this study, for the first time, we investigated the differences in the reactive oxygen species (ROS) reduction abilities of tissue-specific MSCs to mitigate cellular damage in oxidative stress. Hepatic Stellate cells (LX-2) and cardiomyocytes were treated with Antimycin A (AMA) to induce oxidative stress and tissue specific MSCs were co-cultured to study the reduction in ROS levels. We found that both donor's age and source of tissue affected the ability of MSCs to reduce increased ROS levels in damaged cells. In addition, the abilities of same MSCs differed in LX-2 and cardiomyocytes in terms of magnitude of reduction of ROS, suggesting that the type of recipient cells should be kept in consideration when using MSCs in regenerative medicine for treatment purposes.

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Delivery of cellular factors to regulate bone healing.

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Abstract

Bone tissue has a strong intrinsic regenerative capacity, thanks to a delicate and complex interplay of cellular and molecular processes, which tightly involve the immune system. Pathological settings of anatomical, biomechanical or inflammatory nature may lead to impaired bone healing. Innovative strategies to enhance bone repair, including the delivery of osteoprogenitor cells or of potent cytokines/morphogens, indicate the potential of 'orthobiologics', but are not fully satisfactory. Here, we review different approaches based on the delivery of regenerative cues produced by cells but in cell-free, possibly off-the-shelf configurations. Such strategies exploit the paracrine effect of the secretome of mesenchymal stem/stromal cells, presented in soluble form, shuttled through extracellular vesicles, or embedded within the network of extracellular matrix molecules. In addition to osteoinductive molecules, attention is given to factors targeting the resident immune cells, to reshape inflammatory and immunity processes from scarring to regenerative patterns.

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Doxorubicin, mesenchymal stem cell toxicity and antitumour activity: implications for clinical use.

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Abstract

OBJECTIVES:

The use of doxorubicin, an antineoplastic medication used for the treatment of cancers via mechanisms that prevent replication of cells or lead to their death, can result in damage to healthy cells as well as malignant. Among the affected cells are mesenchymal stem cells (MSCs), which are involved in the maintenance and repair of tissues in the body. This review explores the mechanisms of biological effects and damage attributed to doxorubicin on MSCs. The PubMed database was used as a source of literature for this review.

KEY FINDINGS:

Doxorubicin has the potential to lead to significant and irreversible damage to the human bone marrow environment, including MSCs. The primary known mechanism of these changes is through free radical damage and activation of apoptotic pathways. The presence of MSCs in culture or in vivo appears to either suppress or promote tumour growth. Interactions between doxorubicin and MSCs have the potential to increase chemotherapy resistance.

SUMMARY:

Doxorubicin-induced damage to MSCs is of concern clinically. However, MSCs also have been associated with resistance of tumour cells to drugs including doxorubicin. Further studies, particularly in vivo, are needed to provide consistent results of how the doxorubicin-induced changes to MSCs affect treatment and patient health