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Polyphenols from grape pomace induce osteogenic differentiation in mesenchymal stem cells.

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Author information

Abstract

Polyphenols are increasingly investigated for the treatment of periodontitis and research on their use in dental biomaterials is currently being conducted. Grape pomace extracts are a rich source of polyphenols. In the present study, the polyphenols of two different types of grape pomace were characterized and identified by high-performance liquid chromatography-diode array detector, and the effect of polyphenol-rich grape pomace extracts on mesenchymal stem cell (MSC) osteogenic differentiation was investigated. Solid-liquid extraction was used to recover polyphenols from red and white grape pomace. The two extracts have been characterized through the phenolic content and antioxidant power. Human MSCs (hMSCs) from the bone marrow were cultured both with and without given amounts (10 or 20 µg/ml) of the obtained pomace extracts. Their effects on cell differentiation were evaluated by reverse transcription-quantitative polymerase chain reaction, compared with relevant controls. Results showed that both pomace extracts, albeit different in phenolic composition and concentration, induced multiple effects on hMSC gene expression, such as a decreased receptor activator of nuclear factor κ-B ligand/osteoprotegerin ratio and an enhanced expression of genes involved in osteoblast differentiation, thus suggesting a shift of hMSCs towards osteoblast differentiation. The obtained results provided data in favor of the exploitation of polyphenol properties from grape pomace extracts as complementary active molecules for dental materials and devices for bone regeneration in periodontal defects.

Mater Sci Eng C Mater Biol Appl. 2020 Apr;109:110427. doi: 10.1016/j.msec.2019.110427. Epub 2019 Nov 14.

Strontium ion reinforced bioceramic scaffold for load bearing bone regeneration.

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Abstract

Bone defects in load bearing areas require bone reconstruction with strong biomaterial having mechanical characteristics like cortical bone. Bioceramics are biomaterials that support bone formation as well as provide adequate mechanical properties. A strontium substitution of the bioceramic is expected to further increase its bioactivity by enhancing osteogenesis and protect the bone from osteoclastic resorption. The study involves development, characterization and in vivo testing of a newly developed strontium substituted hydroxyapatite based bioceramic scaffold (SrHAB) with sufficient biomechanical properties. Optimal concentration of strontium ion required for enhanced osteogenic

differentiation was identified by comparing three compositions of SrHAB scaffold; namely Sr10HAB, Sr30HAB and Sr50 HAB for their Alkaline phosphatase activity in vitro. The selected Sr10HAB scaffold demonstrated in vivo bone formation with osteogenic differentiation of stromal derived mesenchymal stem cells (MSC) from human and ovine sources in ectopic and ovine models. Thus, Sr10HAB scaffold has a potential for application in load bearing bone requirements of orthopaedics and dentistry.

Front Cell Dev Biol. 2020 Mar 26;8:197. doi: 10.3389/fcell.2020.00197. eCollection 2020.

Human Obesity Induces Dysfunction and Early Senescence in Adipose Tissue-Derived Mesenchymal Stromal/Stem Cells.

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Abstract

BACKGROUND:

Chronic inflammatory conditions like obesity may adversely impact the biological functions underlying the regenerative potential of mesenchymal stromal/stem cells (MSC). Obesity can impair MSC function by inducing cellular senescence, a growth-arrest program that transitions cells to a pro-inflammatory state. However, the effect of obesity on adipose tissue-derived MSC in human subjects remains unclear. We tested the hypothesis that obesity induces senescence and dysfunction in human MSC.

METHODS:

MSC were harvested from abdominal subcutaneous fat collected from obese and age-matched non-obese subjects (n = 40) during bariatric or kidney donation surgeries, respectively. MSC were characterized, their migration and proliferation assessed, and cellular senescence evaluated by gene expression of cell-cycle arrest and senescence-associated secretory phenotype markers. *In vitro* studies tested MSC effect on injured human umbilical vein endothelial cells (HUVEC) function.

RESULTS:

Mean age was 59 ± 8 years, 66% were females. Obese subjects had higher body-mass index (BMI) than non-obese. MSC from obese subjects exhibited lower proliferative capacities than non-obese-MSC, suggesting decreased function, whereas their migration remained unchanged. Senescent cell burden and phenotype, manifested as *p16*, *p53*, *IL-6*, and *MCP-1* gene expression, were significantly upregulated in obese subjects' MSC. BMI correlated directly with expression of *p16*, *p21*, and *IL-6*. Furthermore, co-incubation with non-obese, but not with obese-MSC, restored VEGF expression and tube formation that were blunted in injured HUVEC.

CONCLUSION:

Human obesity triggers an early senescence program in adipose tissue-derived MSC. Thus, obesity-induced cellular injury may alter efficacy of this endogenous repair system and hamper the feasibility of autologous transplantation in obese individuals.

Adv Sci (Weinh). 2020 Feb 11;7(7):1902398. doi: 10.1002/advs.201902398. eCollection 2020 Apr.

Human Platelet Lysates-Based Hydrogels: A Novel Personalized 3D Platform for Spheroid Invasion Assessment.

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Abstract

Fundamental physiologic and pathologic phenomena such as wound healing and cancer metastasis are typically associated with the migration of cells through adjacent extracellular matrix. In recent years, advances in biomimetic materials have supported the progress in 3D cell culture and provided biomedical tools for the development of models to study spheroid invasiveness. Despite this, the exceptional biochemical and biomechanical properties of human-derived materials are poorly explored. Human methacryloyl platelet lysates (PLMA)-based hydrogels are herein proposed as reliable 3D platforms to sustain in vivo-like cell invasion mechanisms. A systematic analysis of spheroid viability, size, and invasiveness is performed in three biomimetic materials: PLMA hydrogels at three different concentrations, poly(ethylene glycol) diacrylate, and Matrigel. Results demonstrate that PLMA hydrogels perfectly support the recapitulation of the tumor invasion behavior of cancer cell lines (MG-63, SaOS-2, and A549) and human bone-marrow mesenchymal stem cell spheroids. The distinct invasiveness ability of each cell type is reflected in the PLMA hydrogels and, furthermore, different mechanical properties produce an altered invasive behavior. The herein presented human PLMA-based hydrogels could represent an opportunity to develop accurate cell invasiveness models and open up new possibilities for humanized and personalized high-throughput screening and validation of anticancer drugs.

Drug Des Devel Ther. 2020 Mar 26;14:1241-1256. doi: 10.2147/DDDT.S243944. eCollection 2020.

Growth Factor Gene-Modified Mesenchymal Stem Cells in Tissue Regeneration.

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Author information

Abstract

There have been marked changes in the field of stem cell therapeutics in recent years, with many clinical trials having been conducted to date in an effort to treat myriad diseases. Mesenchymal stem cells (MSCs) are the cell type most frequently utilized in stem cell therapeutic and tissue regenerative strategies, and have been used with excellent safety to date. Unfortunately, these MSCs have limited ability to engraft and survive, reducing their clinical utility. MSCs are able to secrete growth factors that can support the regeneration of tissues, and engineering MSCs to express such growth factors can improve their survival, proliferation, differentiation, and tissue reconstructing abilities. As such, it is likely that such genetically modified MSCs may represent the next stage of regenerative therapy.

Indeed, increasing volumes of preclinical research suggests that such modified MSCs expressing growth factors can effectively treat many forms of tissue damage. In the present review, we survey recent approaches to producing and utilizing growth factor gene-modified MSCs in the context of tissue repair and discuss its prospects for clinical application.

J Orthop Surg Res. 2020 Apr 9;15(1):137. doi: 10.1186/s13018-020-01664-z.

Intra-articular infiltration of adipose-derived stromal vascular fraction cells slows the clinical progression of moderate-severe knee osteoarthritis: hypothesis on the regulatory role of intra-articular adipose tissue.

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Abstract

BACKGROUND:

The infiltration of the stromal vascular fraction (SVF) of autologous adipose tissue to treat osteoarthritis has been used for several years demonstrating its safety and noticeable efficacy. This article presents clinical data from patients afftected by moderate and severe knee osteoarthritis demonstrating safety and clinical efficacy of the treatment when this autologous cell product is injected in the knee joint and patients evaluated post-operatively after 1 year. However, what do we know about the mechanism that underlies this clinical improvement? This article proposes, for the first time in our opinion, a hypothesis of the mode of action that involves structural and molecular interactions between SVF and infrapatellar fat pad (IFP). As consequence, there would be a re-education of intra-articular adipose tissue, which we consider a key player for the clinical effect observed in the mid and long term mainly due to immuno-regulatory mechanisms.

METHODS:

This is a retrospective and not controlled study that evaluated 50 patients (100 joints) ranging from 50 to 89 years old, separated by age cohorts. Clinical efficacy was assessed using the Lequesne, WOMAC, and VAS scales, by ultrasound control and quantification of the biochemical profiles of synovial fluid.

RESULTS:

There were no serious adverse effects. All the indexes studied showed a significant clinical improvement after 1-year follow-up for all ages and OA degree groups. This finding was correlated with the ultrasound observations and biochemical data, which show a marked decrease in catabolic and pro-inflammatory molecules (MMP-2, IL-1B, IL-6, and IL-8) and significant increase for anabolic and anti-inflammatory molecules (IGF-1 and IL-10).

CONCLUSIONS:

We conclude that intra-articular SVF infiltration for knee OA treatment is safe and effective during 1 year. We propose that applied SVF cells cause a cascade of molecular and structural events that, through complex interactions between IFP and SVF, re-educating the intra-articular fatty tissue towards a homeostatic, protective, and anti-inflammatory function, which will ultimately promote the restructuring and regeneration of damaged tissues.

Eur Rev Med Pharmacol Sci. 2020 Mar;24(6):2886-2892. doi: 10.26355/eurrev_202003_20652.

Downregulation of GNAS inhibits osteogenesis of bone marrow mesenchymal stem cells and promotes osteoporosis through the Wnt pathway.

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Abstract

OBJECTIVE:

This study aims to explore the role of GNAS in accelerating the progression of osteoporosis by inhibiting osteogenesis of BMSCs by the Wnt pathway.

PATIENTS AND METHODS:

GNAS levels in OP tissues and BMSCs undergoing osteogenesis for different time points were detected. Regulatory effects of GNAS on osteogenesis-related gene expressions, ALP activity, capability of mineralization, and activation of the Wnt pathway in BMSCs were assessed through a series of functional experiments. At last, rescue experiments were performed to further verify the significance of the Wnt pathway during GNAS-mediated osteogenesis development.

RESULTS:

GNAS was downregulated in OP tissues relative to normal bone tissues. With the prolongation of osteogenesis, GNAS level gradually increased in BMSCs. Knockdown of GNAS downregulated expression levels of ALP and RUNX2, and attenuated ALP activity and capability of mineralization in BMSCs. GNAS was able to activate the Wnt pathway in BMSCs. Notably, overexpression of Wnt3a could reverse the regulatory effects of GNAS on osteogenesis-related gene expressions, ALP activity, and capability of mineralization in BMSCs.

CONCLUSIONS:

Downregulation of GNAS suppresses osteogenesis of BMSCs through the Wnt pathway, thus aggravating the progression of osteoporosis.

Adv Biosyst. 2019 Dec;3(12). pii: 1900141. doi: 10.1002/adbi.201900141. Epub 2019 Oct 1.

Morphogen Delivery by Osteoconductive Nanoparticles Instructs Stromal Cell Spheroid Phenotype.

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Abstract

Mesenchymal stem/stromal cells (MSCs) exhibit a rapid loss in osteogenic phenotype upon removal of osteoinductive cues, as commonly occurs during transplantation. Osteogenic differentiation can be more effectively but not fully maintained by aggregating MSCs into spheroids. Therefore, the development of effective strategies that prolong the efficacy of inductive growth factors would be advantageous for advancing cell-based therapies. To address this challenge, osteoinductive bone morphogenetic protein-2 (BMP-2) was adsorbed to osteoconductive hydroxyapatite (HA) nanoparticles for incorporation into MSC spheroids. MSC induction was evaluated in osteogenic conditions and retention of the osteogenic phenotype in the absence of other osteogenic cues. HA was more uniformly incorporated into spheroids at lower concentrations, while BMP-2 dosage was dependent upon initial morphogen concentration. MSC spheroids containing BMP-2-loaded HA nanoparticles exhibited greater alkaline phosphatase (ALP) activity and more uniform spatial expression of osteocalcin compared to spheroids with uncoated HA nanoparticles. Spheroids cultured in media containing soluble BMP-2 demonstrated differentiation only at the spheroid periphery. Furthermore, the osteogenic phenotype of MSC spheroids was better retained with BMP-2-laden HA upon the removal of soluble osteogenic cues. These findings represent a promising strategy for simultaneous delivery of osteoconductive and osteoinductive signals for enhancing MSC participation in bone formation.

World J Stem Cells. 2020 Mar 26;12(3):168-177. doi: 10.4252/wjsc.v12.i3.168.

Mesenchymal stem cells in neurodegenerative diseases: Opinion review on ethical dilemmas.

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Abstract

The treatment of neurodegenerative diseases presents a growing need for innovation in relation to recent evidence in the field of reconstructive therapy using stem cells. Understanding the molecular mechanisms underlying neurodegenerative disorders, and the advent of methods able to induce neuronal stem cell differentiation allowed to develop innovative therapeutic approaches offering the prospect of healthy and perfectly functional cell transplants, able to replace the sick ones. Hence the importance of deepening the state of the art regarding the clinical applications of advanced cell therapy products for the regeneration of nerve tissue. Besides representing a promising area of tissue transplant surgery and a great achievement in the field of neurodegenerative disease, stem cell research presents certain critical issues that need to be carefully examined from the ethical perspective. In fact, a subject so complex and not entirely explored requires a detailed scientific and ethical evaluation aimed at avoiding improper and ineffective use, rather than incorrect indications, technical inadequacies, and incongruous expectations. In fact, the clinical usefulness of stem cells will only be certain if able to provide the patient with safe, long-term and substantially more effective strategies than any other treatment available. The present paper provides an ethical assessment of tissue regeneration

through mesenchymal stem cells in neurodegenerative diseases with the aim to rule out the fundamental issues related to research and clinical translation.

Front Immunol. 2020 Mar 20;11:422. doi: 10.3389/fimmu.2020.00422. eCollection 2020.

Extracellular Vesicles After Allogeneic Hematopoietic Cell Transplantation: Emerging Role in Post-Transplant Complications.

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Abstract

Extracellular vesicles (EVs) play an important role in the cellular crosstalk by transferring bioactive molecules through biological barriers from a cell to another, thus influencing recipient cell functions and phenotype. Therefore, EVs are increasingly being explored as biomarkers of disease progression or response to therapy and as potential therapeutic agents in different contexts including in hematological malignancies. Recently, an EV role has emerged in allogeneic hematopoietic cell transplantation (allo-HCT) as well. Allogeneic hematopoietic cell transplantation often represents the only curative option in several hematological disorders, but it is associated with potentially life-threatening complications that can have a significant impact on clinical outcomes. The most common complications have been well-established and include graft-versus-host disease and infections. Furthermore, relapse remains an important cause of treatment failure. The aim of this review is to summarize the current knowledge, the potential applications, and clinical relevance of EVs in allo-HCT. Herein, we will mainly focus on the immune-modulating properties of EVs, in particular those derived from mesenchymal stromal cells, as potential therapeutic strategy to improve allo-HCT outcome. Moreover, we will briefly describe the main findings on EVs as biomarkers to monitor graft-versus-host disease onset and tumor relapse.

Biomaterials. 2020 Apr 1;247:119998. doi: 10.1016/j.biomaterials.2020.119998. [Epub ahead of print]

Characterisation and evaluation of the regenerative capacity of Stro-4+ enriched bone marrow mesenchymal stromal cells using bovine extracellular matrix hydrogel and a novel biocompatible melt electro-written medical-grade polycaprolactone scaffold.

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Author information

Abstract

Many skeletal tissue regenerative strategies centre around the multifunctional properties of bone marrow derived stromal cells (BMSC) or mesenchymal stem/stromal cells (MSC)/bone marrow derived skeletal stem cells (SSC). Specific identification of these particular stem cells has been inconclusive.

However, enriching these heterogeneous bone marrow cell populations with characterised skeletal progenitor markers has been a contributing factor in successful skeletal bone regeneration and repair strategies. In the current studies we have isolated, characterised and enriched ovine bone marrow mesenchymal stromal cells (oBMSCs) using a specific antibody, Stro-4, examined their multipotential differentiation capacity and, in translational studies combined Stro-4+ oBMSCs with a bovine extracellular matrix (bECM) hydrogel and a biocompatible melt electro-written medical-grade polycaprolactone scaffold, and tested their bone regenerative capacity in a small in vivo, highly vascularised, chick chorioallantoic membrane (CAM) model and a preclinical, critical-sized ovine segmental tibial defect model. Proliferation rates and CFU-F formation were similar between unselected and Stro-4+ oBMSCs. Col1A1, Col2A1, mSOX-9, PPARG gene expression were upregulated in respective osteogenic, chondrogenic and adipogenic culture conditions compared to basal conditions with no significant difference between Stro-4+ and unselected oBMSCs. In contrast, proteoglycan expression, alkaline phosphatase activity and adipogenesis were significantly upregulated in the Stro-4+ cells. Furthermore, with extended cultures, the oBMSCs had a predisposition to maintain a strong chondrogenic phenotype. In the CAM model Stro-4+ oBMSCs/bECM hydrogel was able to induce bone formation at a femur fracture site compared to bECM hydrogel and control blank defect alone. Translational studies in a critical-sized ovine tibial defect showed autograft samples contained significantly more bone, (4250.63 mm^3, SD = 1485.57) than blank (1045.29 mm^3, SD = 219.68) ECM-hydrogel (1152.58 mm^3, SD = 191.95) and Stro-4+/ECM-hydrogel (1127.95 mm^3, SD = 166.44) groups. Stro-4+ oBMSCs demonstrated a potential to aid bone repair in vitro and in a small in vivo bone defect model using select scaffolds. However, critically, translation to a large related preclinical model demonstrated the complexities of bringing small scale reported stem-cell material therapies to a clinically relevant model and thus facilitate progression to the clinic.

Elife. 2020 Mar 30;9. pii: e54523. doi: 10.7554/eLife.54523.

Increase of circulating IGFBP-4 following genotoxic stress and its implication for senescence.

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Abstract

Senescent cells secrete several molecules, collectively named *senescence-associated secretory phenotype* (SASP). In the SASP of cells that became senescent following several in vitro chemical and physical stress, we identified the IGFBP-4 protein that can be considered a general stress mediator. This factor appeared to play a key role in senescence-paracrine signaling. We provided evidences showing that genotoxic injury, such as low dose irradiation, may promote an IGFBP-4 release in bloodstream both in mice irradiated with 100 mGy X-ray and in human subjects that received Computer Tomography. Increased level of circulating IGFBP-4 may be responsible of pro-aging effect. We found a significant increase of senescent cells in the lungs, heart, and kidneys of mice that were

intraperitoneally injected with IGFBP-4 twice a week for two months. We then analyzed how genotoxic stressors may promote the release of IGFBP-4 and the molecular pathways associated with the induction of senescence by this protein.