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Non-Ionizing Radiation for Cardiac Human Amniotic Mesenchymal Stromal Cell Commitment: A Physical Strategy in Regenerative Medicine.

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Author information

Abstract

Cell therapy is an innovative strategy for tissue repair, since adult stem cells could have limited regenerative ability as in the case of myocardial damage. This leads to a local contractile dysfunction due to scar formation. For these reasons, refining strategy approaches for "in vitro" stem cell commitment, preparatory to the "in vivo" stem cell differentiation, is imperative. In this work, we isolated and characterized at molecular and cellular level, human Amniotic Mesenchymal Stromal Cells (hAMSCs) and exposed them to a physical Extremely Low Frequency Electromagnetic Field (ELF-EMF) stimulus and to a chemical Nitric Oxide treatment. Physically exposed cells showed a decrease of cell proliferation and no change in metabolic activity, cell vitality and apoptotic rate. An increase in the mRNA expression of cardiac and angiogenic differentiation markers, confirmed at the translational level, was also highlighted in exposed cells. Our data, for the first time, provide evidence that physical ELF-EMF stimulus (7 Hz, 2.5 μT), similarly to the chemical treatment, is able to trigger hAMSC cardiac commitment. More importantly, we also observed that only the physical stimulus is able to induce both types of commitments contemporarily (cardiac and angiogenic), suggesting its potential use to obtain a better regenerative response in cell-therapy protocols.

Hum Immunol. 2018 Aug 14. pii: S0198-8859(18)30208-8. doi: 10.1016/j.humimm.2018.08.006. [Epub ahead of print]

Human Herpes Simplex 1 Virus infection of endometrial decidual tissue-derived MSC alters HLA-G expression and immunosuppressive functions.

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Abstract

OBJECTIVES:

Mesenchymal stromal/stem cells have immunosuppressive functions. Our previous results demonstrated that one of the players of this immunomodulation can be ascribed to the Human Leukocyte Antigen-G. HLA-G, a non classical HLA class I antigen, is involved in immune tolerance during pregnancy, organ transplantation, autoimmune and inflammatory diseases. In this study we wanted to verify whether human endometrial decidual tissue derived (EDT)-MSC could express HLA-G.

Additionally we assessed the permissivity to Human Herpesvirus infections, using HSV-1 as a model, and the possible effect on EDT-MSC immunosuppressive functions towards peripheral blood mononuclear cell (PBMC) proliferation.

METHODS:
We analyzed immune-inhibitory functions and HLA-G expression in human EDT-MSC before and after HSV-1 infection.

RESULTS:
We observed that EDT-MSC express HLA-G molecules, that partly are responsible for the immune-inhibitory functions of EDT-MSC towards PBMC proliferation. EDT-MSC are permissive for a productive infection by HSV-1, that decreases HLA-G expression and affects EDT-MSC immune-inhibitory functions.

CONCLUSIONS:
We demonstrate that EDT-MSC are susceptible to HSV-1 infection, that reduces HLA-G expression and their immune-inhibitory function. These data could have a clinical implication in the use of EDT-MSC as an immunosuppressant, in particular in steroid-refractory GvHD after allogeneic hematopoietic stem cell transplantation and in autoimmune diseases.

Biogerontology. 2018 Aug 12. doi: 10.1007/s10522-018-9766-4. [Epub ahead of print]

Detecting senescent fate in mesenchymal stem cells: a combined cytofluorimetric and ultrastructural approach.

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Abstract

Senescence can impair the therapeutic potential of stem cells. In this study, senescence-associated morphofunctional changes in periosteum-derived progenitor cells (PDPCs) from old and young individuals were investigated by combining cytofluorimetry, immunohistochemistry, and transmission electron microscopy. Cell cycle analysis demonstrated a large number of G0/G1 phase cells in PDPCs from old subjects and a progressive accumulation of G0/G1 cells during passaging in cultures from young subjects. Cytofluorimetry documented significant changes in light scattering parameters and closely correlated with the ultrastructural features, especially changes in mitochondrial shape and autophagy, which are consistent with the mitochondrial-lysosomal axis theory of ageing. The combined morphological, biofunctional, and ultrastructural approach enhanced the flow cytometric study of PDPC ageing. We speculate that impaired autophagy, documented in replicative senescent and old PDPCs, reflect a switch from quiescence to senescence. Its demonstration in a tissue with limited turnover-like the cambium layer of the periosteum, where reversible quiescence is the normal stem cell state throughout life-adds a new piece to the regenerative medicine jigsaw in an ageing society.

Oncotarget. 2017 Feb 7;8(6):9608-9616. doi: 10.18632/oncotarget.14155.

The tumor microenvironment promotes cancer progression and cell migration.

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Author information

Abstract

The tumor microenvironment contributes to cancer progression, in part through interactions between tumor and normal stromal cells. This study analyzed morphological and molecular changes induced in co-cultured human fibroblasts (HFs) and the MG-63 osteosarcoma cell line. Co-cultured cell monolayers were morphologically analyzed using high resolution scanning electron microscopy (HR-SEM), and trans-well assays were performed to assess cell migration and invasion. Proteins involved in inflammatory responses, cancer cell invasion, and angiogenesis were assessed using western blotting. HR-SEM showed progressive spatial orientation loss by fibroblasts in contact with MG-63s, while MG-63s proliferated rapidly and invaded HF space. Trans-well assays showed enhanced MG-63 migration in the presence of HFs. IL-6 expression was increased in co-cultured HFs, possibly stimulated by TNF-α. HFs do not normally express YKL-40 but did so in co-culture. Band densitometric analyses showed that increasing YKL-40 expression was followed by VEGF overexpression, especially in MG-63s. Finally, our results confirmed fibroblasts as the main matrix metalloproteinase source in this tumor microenvironment. Our study sheds new light on how tumor-stroma interactions promote tumor development and progression, and may support identification of novel anti-cancer therapeutics.

Curr Res Transl Med. 2018 Aug 10. pii: S2452-3186(18)30034-5. doi: 10.1016/j.retram.2018.06.002. [Epub ahead of print]

Adipose tissue-derived mesenchymal stromal cells for clinical application: An efficient isolation approach.

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Author information

Abstract

PURPOSE OF THE STUDY:

Mesenchymal stromal cells (MSCs) are considered a promising tool for cell therapy approaches. The translation of research-based cell culture protocols into procedures that comply with Good Manufacturing Practice (GMP) is critical. The aim of this study was to design a new method for the expansion of MSCs from Adipose Tissue (AT-MSCs) in compliance with GMP, without enzymatic tissue digestion and without the use of animal proteins as source of growth factors.

PATIENTS AND METHODS:

MSCs were expanded from 10 periumbilical biopsies. Our new isolation approach is based on: (1) disruption of AT with an automated, closed system; (2) use of GMP-grade medium without the addition of fetal bovine serum or platelet lysate; (3) use of human recombinant Trypsin. AT-MSCs cultured in α-MEM and minced by scalpel were used as control.

RESULTS:

It was possible to expand MSCs from all the AT-samples for at least eight passages. MSCs displayed the typical spindle-shape morphology, a high viability, multilineage differentiation potential and high expression levels of the typical MSC-specific surface antigens and genes. Compared to standard method, MSCs obtained with the new method showed higher yield, up to passage 6, and higher purity in terms of percentage of CD34 and CD45 markers. All AT-MSCs exhibit in vitro immunosuppressive capacity and possess a normal karyotype.

CONCLUSIONS:

Our data clearly demonstrate that our new approach permits to generate AT-MSCs fully compliant for therapeutic use and better at least in terms of quantity and purity than those obtained with the standard method.

J Pediatr Hematol Oncol. 2018 Aug 14. doi: 10.1097/MPH.0000000000001281. [Epub ahead of print]

In Vitro Mesenchymal Progenitor Cell Expansion is a Predictor of Transplant-related Mortality and acute GvHD III-IV After Bone Marrow Transplantation in Univariate Analysis: A Large Single-Center Experience.

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Abstract

Mesenchymal stromal cells (MSCs) are multipotent stem cells able to differentiate into mesenchymal origin tissue and support the growth of hematopoietic stem cells. In order to understand the role of MSCs infused in bone marrow grafts, 53 consecutive patients were analyzed for engraftment, acute and chronic graft-versus-host disease (GvHD), transplant-related mortality (TRM), relapse incidence, and overall survival. The MSC content was measured as MSC expansion at the second passage. When in vitro-expanded MSC (cumulative population doubling at second passage, cPDp2) values were stratified according to the median value (2.2-fold increase), the univariate analysis showed a significant difference in TRM (23% vs. 3.8%, P=0.05.) and in acute GvHD III-IV incidence (12% vs. 4%, P=0.04), while the multivariate analysis did not confirm its independent role. No clinical parameters in donors and recipients were identified as predictors of cPDp2 expansion. Our study suggests a role for short-term ex vivo-expanded MSCs in reduced aGVHD III-IV incidence and TRM in univariate analysis. A multicenter, larger study is warranted to confirm these data.

Mol Cancer. 2018 Aug 15;17(1):122. doi: 10.1186/s12943-018-0867-0.

Exosomes derived from mesenchymal stem cells enhance radiotherapy-induced cell death in tumor and metastatic tumor foci.

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Author information

Abstract

BACKGROUND:

We have recently shown that radiotherapy may not only be a successful local and regional treatment but, when combined with MSCs, may also be a novel systemic cancer therapy. This study aimed to investigate the role of exosomes derived from irradiated MSCs in the delay of tumor growth and metastasis after treatment with MSC + radiotherapy (RT).

METHODS:

We have measured tumor growth and metastasis formation, of subcutaneous human melanoma A375 xenografts on NOD/SCID-gamma mice, and the response of tumors to treatment with radiotherapy (2 Gy), mesenchymal cells (MSC), mesenchymal cells plus radiotherapy, and without any treatment. Using proteomic analysis, we studied the cargo of the exosomes released by the MSC treated with 2 Gy, compared with the cargo of exosomes released by MSC without treatment.

RESULTS:

The tumor cell loss rates found after treatment with the combination of MSC and RT and for exclusive RT, were: 44.4% % and 12,1%, respectively. Concomitant and adjuvant use of RT and MSC, increased the mice surviving time 22,5% in this group, with regard to the group of mice treated with exclusive RT and in a 45,3% respect control group. Moreover, the number of metastatic foci found in the internal organs of the mice treated with MSC + RT was 60% less than the mice group treated with RT alone. We reasoned that the exosome secreted by the MSC, could be implicated in tumor growth delay and metastasis control after treatment.

CONCLUSIONS:

Our results show that exosomes derived form MSCs, combined with radiotherapy, are determinant in the enhancement of radiation effects observed in the control of metastatic spread of melanoma cells and suggest that exosome-derived factors could be involved in the bystander, and abscopal effects found after treatment of the tumors with RT plus MSC. Radiotherapy itself may not be systemic, although it might contribute to a systemic effect when used in combination with mesenchymal stem cells owing the ability of irradiated MSCs-derived exosomes to increase the control of tumor growth and metastasis.

Front Bioeng Biotechnol. 2018 Jul 31;6:105. doi: 10.3389/fbioe.2018.00105. eCollection 2018.

Tissue Engineering and Cell-Based Therapies for Fractures and Bone Defects.

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Author information

Abstract

Bone fractures and segmental bone defects are a significant source of patient morbidity and place a staggering economic burden on the healthcare system. The annual cost of treating bone defects in the US has been estimated to be $5 billion, while enormous costs are spent on bone grafts for bone injuries, tumors, and other pathologies associated with defective fracture healing. Autologous bone grafts represent the gold standard for the treatment of bone defects. However, they are associated with variable clinical outcomes, postsurgical morbidity, especially at the donor site, and increased surgical costs. In an effort to circumvent these limitations, tissue engineering and cell-based therapies have been proposed as alternatives to induce and promote bone repair. This review focuses on the recent advances in bone tissue engineering (BTE), specifically looking at its role in treating delayed fracture healing (non-unions) and the resulting segmental bone defects. Herein we discuss: (1) the processes of endochondral and intramembranous bone formation; (2) the role of stem cells, looking specifically at mesenchymal (MSC), embryonic (ESC), and induced pluripotent (iPSC) stem cells as viable building blocks to engineer bone implants; (3) the biomaterials used to direct tissue growth, with a focus on ceramic, biodegradable polymers, and composite materials; (4) the growth factors and molecular signals used to induce differentiation of stem cells into the osteoblastic lineage, which ultimately leads to active bone formation; and (5) the mechanical stimulation protocols used to maintain the integrity of the bone repair and their role in successful cell engraftment. Finally, a couple clinical scenarios are presented (non-unions and avascular necrosis-AVN), to illustrate how novel cell-based therapy approaches can be used. A thorough understanding of tissue engineering and cell-based therapies may allow for better incorporation of these potential therapeutic approaches in bone defects allowing for proper bone repair and regeneration.

Stem Cell Res Ther. 2018 Aug 14;9(1):220. doi: 10.1186/s13287-018-0960-8.

Therapeutic potential of stromal cells of non-renal or renal origin in experimental chronic kidney disease.

Rota C[1], Morigi M[2], Cerullo D[1], Introna M[3], Colpani O[1], Corna D[1], Capelli C[3], Rabelink TJ[4], Leuning DG[4], Rottoli D[1], Benigni A[1], Zoja C[1], Remuzzi G[1,5,6].

Author information

Abstract

BACKGROUND:

Mesenchymal stromal cell (MSC)-based therapy is a promising strategy for preventing the progression of chronic kidney disease (CKD), with the potential to induce tissue regeneration. In search of the best cellular source we compared, in the rat model of adriamycin (ADR) nephropathy, the regenerative potential of human stromal cells of non-renal origin, such as bone marrow (bm) MSCs and umbilical

cord (uc) MSCs, with that of newly discovered stromal cells of renal origin, the kidney perivascular cells (kPSCs) known to exhibit tissue-specific properties.

METHODS:

The therapeutic effect of repeated infusions of human bmMSCs, ucMSCs, kPSCs (1.5×10^6 cells/rats) or conditioned medium from ucMSCs was studied in athymic rats with ADR-induced nephropathy (7.9 mg/kg). The ability of the three stromal cell populations to engraft the damaged kidney was evaluated by detecting the presence of human nuclear antigen^{pos} cells. Glomerular podocyte loss and endothelial damage, sclerotic lesions and inflammation were assessed at 14 and 28 days. In-vitro experiments with a transwell system were performed to investigate the effects of different stromal cell populations on parietal epithelial cells (PECs) activated or not with albumin or angiotensin II for 24 h.

RESULTS:

Infusions of non-renal and renal stromal cells resulted in a comparable engraftment into the kidney, in the peritubular areas and around the glomerular structures. All three cell populations limited podocyte loss and glomerular endothelial cell injury, and attenuated the formation of podocyte and PEC bridges. This translated into a reduction of glomerulosclerosis and fibrosis. Human ucMSCs had an anti-inflammatory effect superior to that of the other stromal cells, reducing macrophage infiltration and inducing polarisation towards the M2 macrophage phenotype. Conditioned medium from ucMSCs shared the same renoprotective effects of the cells. Consistent with in-vivo data, bmMSCs and kPSCs, but even more so ucMSCs, limited proliferation, migratory potential and extracellular matrix production of activated PECs, when cultured in a transwell system.

CONCLUSIONS:

Our data indicate that either non-renal or renal stromal cells induce renal tissue repair, highlighting ucMSCs and their conditioned medium as the most reliable clinical therapeutic tool for CKD patients.

Vet J. 2018 Aug;238:49-57. doi: 10.1016/j.tvjl.2018.07.004. Epub 2018 Jul 17.

Practical considerations for clinical use of mesenchymal stem cells: From the laboratory to the horse.

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Author information

Abstract

Since the clinical use of mesenchymal stem cells (MSCs) for treating musculoskeletal injuries is gaining popularity, practitioners should be aware of the factors that may affect MSCs from tissue harvesting for MSC isolation to cell delivery into the injury site. This review provides equine practitioners with up-to-date, practical knowledge for the treatment of equine patients using MSCs. A brief overview of laboratory procedures affecting MSCs is provided, but the main focus is on shipping conditions, routes of administration, injection methods, and which commonly used products can be combined with MSCs and which products should be avoided as they have deleterious effects on cells. There are still several knowledge gaps regarding MSC-based therapies in horses. Therefore, it is important to properly

manage the factors which are currently known to affect MSCs, to further strengthen the evidence basis of this treatment.

Biomaterials. 2018 Jul 11;181:333-346. doi: 10.1016/j.biomaterials.2018.07.016. [Epub ahead of print]

Large-scale production of stem cells utilizing microcarriers: A biomaterials engineering perspective from academic research to commercialized products.

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Author information

Abstract

Human stem cells, including pluripotent, embryonic and mesenchymal, stem cells play pivotal roles in cell-based therapies. Over the past decades, various methods for expansion and differentiation of stem cells have been developed to satisfy the burgeoning clinical demands. One of the most widely endorsed technologies for producing large cell quantities is using microcarriers (MCs) in bioreactor culture systems. In this review, we focus on microcarriers properties that can manipulate the expansion and fate of stem cells. Here, we provide an overview of commercially available MCs and focus on novel stimulus responsive MCs controlled by temperature, pH and field changes. Different features of MCs including composition, surface coating, morphology, geometry/size, surface functionalization, charge and mechanical properties, and their cellular effects are also highlighted. We then conclude with current challenges and outlook on this promising technology.

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Mesenchymal Stem Cell Migration during Bone Formation and Bone Diseases Therapy.

Su P[1,2,3], Tian Y[4,5,6], Yang C[7,8,9], Ma X[10,11,12], Wang X[13,14,15], Pei J[16,17,18], Qian A[19,20,21].
Author information

Abstract

During bone modeling, remodeling, and bone fracture repair, mesenchymal stem cells (MSCs) differentiate into chondrocyte or osteoblast to comply bone formation and regeneration. As multipotent stem cells, MSCs were used to treat bone diseases during the past several decades. However, most of these implications just focused on promoting MSC differentiation. Furthermore, cell migration is also a key issue for bone formation and bone diseases treatment. Abnormal MSC migration could cause different kinds of bone diseases, including osteoporosis. Additionally, for bone disease treatment, the migration of endogenous or exogenous MSCs to bone injury sites is required. Recently, researchers have paid more and more attention to two critical points. One is how to apply MSC migration to bone disease therapy. The other is how to enhance MSC migration to improve the therapeutic efficacy of bone diseases. Some considerable outcomes showed that enhancing MSC migration might be a novel trick for reversing bone loss and other bone diseases, such as osteoporosis, fracture, and osteoarthritis (OA). Although plenty of challenges need to be conquered, application of endogenous and exogenous

MSC migration and developing different strategies to improve therapeutic efficacy through enhancing MSC migration to target tissue might be the trend in the future for bone disease treatment.