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Reciprocal modulation of mesenchymal stem cells and tumor cells promotes lung cancer metastasis.

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Abstract

Metastasis is a multi-step process in which direct crosstalk between cancer cells and their microenvironment plays a key role. Here, we assessed the effect of paired tumor-associated and normal lung tissue mesenchymal stem cells (MSCs) on the growth and dissemination of primary human lung carcinoma cells isolated from the same patients. We show that the tumor microenvironment modulates MSC gene expression and identify a four-gene MSC signature that is functionally implicated in promoting metastasis. We also demonstrate that tumor-associated MSCs induce the expression of genes associated with an aggressive phenotype in primary lung cancer cells and selectively promote their dissemination rather than local growth. Our observations provide insight into mechanisms by which the stroma promotes lung cancer metastasis.

[Int J Mol Sci](#). 2018 Mar 1;19(3). pii: E707. doi: 10.3390/ijms19030707.

Comparison of Tumor- and Bone Marrow-Derived Mesenchymal Stromal/Stem Cells from Patients with High-Grade Osteosarcoma.

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Abstract

Osteosarcoma (OS) is suspected to originate from dysfunctional mesenchymal stromal/stem cells (MSC). We sought to identify OS-derived cells (OSDC) with potential cancer stem cell (CSC) properties by comparing OSDC to MSC derived from bone marrow of patients. This study included in vitro characterization with sphere forming assays, differentiation assays, cytogenetic analysis, and in vivo investigations of their tumorigenicity and tumor supportive capacities. Primary cell lines were isolated from nine high-grade OS samples. All primary cell lines demonstrated stromal cell characteristics. Compared to MSC, OSDC presented a higher ability to form sphere clones, indicating a potential CSC phenotype, and were more efficient at differentiation towards osteoblasts. None of the OSDC displayed the complex chromosome rearrangements typical of high grade OS and none of them induced tumors in immunodeficient mice. However, two OSDC demonstrated focused genomic abnormalities. Three out of seven, and six out of seven OSDC showed a supportive role on local tumor development, and on

metastatic progression to the lungs, respectively, when co-injected with OS cells in nude mice. The observation of OS-associated stromal cells with rare genetic abnormalities and with the capacity to sustain tumor progression may have implications for future tumor treatments.

[Stem Cell Res Ther.](#) 2018 Mar 9;9(1):63. doi: 10.1186/s13287-018-0791-7.

Mesenchymal stem cell-derived extracellular vesicles: novel frontiers in regenerative medicine.

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Abstract

Mesenchymal stem cells (MSCs) are multipotent stem cells that have gained significant attention in the field of regenerative medicine. The differentiation potential along with paracrine properties of MSCs have made them a key option for tissue repair. The paracrine functions of MSCs are applied through secreting soluble factors and releasing extracellular vesicles like exosomes and microvesicles.

Extracellular vesicles are predominantly endosomal in origin and contain a cargo of miRNA, mRNA, and proteins that are transferred from their original cells to target cells. Recently it has emerged that extracellular vesicles alone are responsible for the therapeutic effect of MSCs in plenty of animal diseases models. Hence, MSC-derived extracellular vesicles may be used as an alternative MSC-based therapy in regenerative medicine. In this review we discuss MSC-derived extracellular vesicles and their therapeutic potential in various diseases.

[Beilstein J Nanotechnol.](#) 2018 Jan 29;9:321-332. doi: 10.3762/bjnano.9.32. eCollection 2018.

Nanoparticle delivery to metastatic breast cancer cells by nanoengineered mesenchymal stem cells.

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Abstract

We created a 3D cell co-culture model by combining nanoengineered mesenchymal stem cells (MSCs) with the metastatic breast cancer cell line MDA-MD-231 and primary breast cancer cell line MCF7 to explore the transfer of quantum dots (QDs) to cancer cells. First, the optimal conditions for high-content QD loading in MSCs were established. Then, QD uptake in breast cancer cells was assessed after 24 h in a 3D co-culture with nanoengineered MSCs. We found that incubation of MSCs with QDs in a serum-free medium provided the best accumulation results. It was found that 24 h post-labelling QDs were eliminated from MSCs. Our results demonstrate that breast cancer cells efficiently uptake QDs that are released from nanoengineered MSCs in a 3D co-culture. Moreover, the uptake is considerably enhanced in metastatic MDA-MB-231 cells compared with MCF7 primary breast cancer cells. Our findings suggest that nanoengineered MSCs could serve as a vehicle for targeted drug delivery to metastatic cancer.

[Front Immunol.](#) 2018 Feb 19;9:262. doi: 10.3389/fimmu.2018.00262. eCollection 2018.

How to Hit Mesenchymal Stromal Cells and Make the Tumor Microenvironment Immunostimulant Rather Than Immunosuppressive.

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Abstract

Experimental evidence indicates that mesenchymal stromal cells (MSCs) may regulate tumor microenvironment (TME). It is conceivable that the interaction with MSC can influence neoplastic cell functional behavior, remodeling TME and generating a tumor cell niche that supports tissue neovascularization, tumor invasion and metastasization. In addition, MSC can release transforming growth factor-beta that is involved in the epithelial-mesenchymal transition of carcinoma cells; this transition is essential to give rise to aggressive tumor cells and favor cancer progression. Also, MSC can both affect the anti-tumor immune response and limit drug availability surrounding tumor cells, thus creating a sort of barrier. This mechanism, in principle, should limit tumor expansion but, on the contrary, often leads to the impairment of the immune system-mediated recognition of tumor cells. Furthermore, the cross-talk between MSC and anti-tumor lymphocytes of the innate and adaptive arms of the immune system strongly drives TME to become immunosuppressive. Indeed, MSC can trigger the generation of several types of regulatory cells which block immune response and eventually impair the elimination of tumor cells. Based on these considerations, it should be possible to favor the anti-tumor immune response acting on TME. First, we will review the molecular mechanisms involved in MSC-mediated regulation of immune response. Second, we will focus on the experimental data supporting that it is possible to convert TME from immunosuppressive to immunostimulant, specifically targeting MSC.

[Knee Surg Sports Traumatol Arthrosc.](#) 2018 Mar 6. doi: 10.1007/s00167-018-4883-9. [Epub ahead of print]

Intra-articular injections of expanded mesenchymal stem cells with and without addition of platelet-rich plasma are safe and effective for knee osteoarthritis.

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Abstract

PURPOSE:

To compare the effectiveness and safety of intra-articular injections of autologous expanded mesenchymal stromal stem cells alone (MSCs), or in combination with platelet-rich plasma (MSCs + PRP), in patients with knee osteoarthritis.

METHODS:

Eighteen patients (57.6 ± 9.6 years) with radiographic symptomatic knee osteoarthritis (Dejour grades II-IV) were randomized to receive intra-articular injections of MSCs (n = 9) or MSCs + PRP (n = 9).

Injections were performed 2-3 weeks after bone marrow aspiration (\pm 80-100 ml) which was obtained from both posterior iliac crests.

RESULTS:

The Knee Injury and Osteoarthritis Outcome Score (KOOS) improved significantly throughout the 12 months for both groups ($p < 0.05$). No statistically significant differences between groups were found in KOOS subscales and global score improvements at 12-month end-point (n.s.). The MSCs group showed significant improvements in the pain, function and daily living activities, and sports and recreational activities subscales ($p < 0.05$). Similarly, the MSCs + PRP group showed significant improvements in the pain, function and daily living activities and quality of life subscales ($p < 0.05$). The average number of fibroblast colony forming units (CFU-F) was 56.8 ± 21.9 for MSCs group and 50.7 ± 21.7 for MSCs + PRP group. Minimal adverse effects were seen in both groups (10 adverse events, in 5 patients).

CONCLUSIONS:

Intra-articular injections of expanded MSCs alone or in combination with PRP are safe and have a beneficial effect on symptoms in patients with symptomatic knee osteoarthritis. Adding PRP to the MSCs injections did not provide additional benefit. These results are encouraging and support the recommendation of this minimally invasive procedure in patients with knee osteoarthritis, without requiring hospitalization. The CFU-F results may be used as reference for future research.

[Regen Med.](#) 2018 Mar 6. doi: 10.2217/rme-2017-0078. [Epub ahead of print]

Biosafety and bioefficacy assessment of human mesenchymal stem cells: what do we know so far?

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Author information

Abstract

An outstanding amount of resources has been used in research on manipulation of human stem cells, especially mesenchymal stem cells (MSCs), for various clinical applications. However, human MSCs have not been fully utilized in clinical applications due to restrictions with regard to their certain biosafety and bioefficacy concerns, for example, genetic abnormality, tumor formation, induction of host immune response and failure of homing and engraftment. This review summarizes the biosafety and bioefficacy assessment of human MSCs in terms of genetic stability, tumorigenicity, immunogenicity, homing and engraftment. The strategies used to reduce the biosafety concerns and improve the bioefficacy of human MSCs are highlighted. In addition, the approaches that can be implemented to improve their biosafety and bioefficacy assessment are briefly discussed.

[Stem Cell Rev.](#) 2018 Mar 5. doi: 10.1007/s12015-018-9803-3. [Epub ahead of print]

Wharton's Jelly Derived Mesenchymal Stem Cells: Comparing Human and Horse.

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Abstract

Wharton's jelly (WJ) is an important source of mesenchymal stem cells (MSCs) both in human and other animals. The aim of this study was to compare human and equine WJMSCs. Human and equine WJMSCs were isolated and cultured using the same protocols and culture media. Cells were characterized by analysing morphology, growth rate, migration and adhesion capability, immunophenotype, differentiation potential and ultrastructure. Results showed that human and equine WJMSCs have similar ultrastructural details connected with intense synthetic and metabolic activity, but differ in growth, migration, adhesion capability and differentiation potential. In fact, at the scratch assay and transwell migration assay, the migration ability of human WJMSCs was higher ($P < 0.05$) than that of equine cells, while the volume of spheroids obtained after 48 h of culture in hanging drop was larger than the volume of equine ones ($P < 0.05$), demonstrating a lower cell adhesion ability. This can also be revealed in the lower doubling time of equine cells (3.5 ± 2.4 days) as compared to human (6.5 ± 4.3 days) ($P < 0.05$), and subsequently in the higher number of cell doubling after 44 days of culture observed for the equine (20.3 ± 1.7) as compared to human cells (8.7 ± 2.4) ($P < 0.05$), and to the higher ($P < 0.05$) ability to form fibroblast colonies at P3. Even if in both species tri-lineage differentiation was achieved, equine cells showed an higher chondrogenic and osteogenic differentiation ability ($P < 0.05$). Our findings indicate that, although the ultrastructure demonstrated a staminal phenotype in human and equine WJMSCs, they showed different properties reflecting the different sources of MSCs.

[Theranostics](#). 2018 Feb 3;8(5):1399-1410. doi: 10.7150/thno.21072. eCollection 2018.

Mesenchymal stem cells-derived exosomes are more immunosuppressive than microparticles in inflammatory arthritis.

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Abstract

Objectives: Mesenchymal stem cells (MSCs) release extracellular vesicles (EVs) that display a therapeutic effect in inflammatory disease models. Although MSCs can prevent arthritis, the role of MSCs-derived EVs has never been reported in rheumatoid arthritis. This prompted us to compare the function of exosomes (Exos) and microparticles (MPs) isolated from MSCs and investigate their immunomodulatory function in arthritis. **Methods:** MSCs-derived Exos and MPs were isolated by differential ultracentrifugation. Immunosuppressive effects of MPs or Exos were investigated on T and B lymphocytes *in vitro* and in the Delayed-Type Hypersensitivity (DTH) and Collagen-Induced Arthritis (CIA) models. **Results:** Exos and MPs from MSCs inhibited T lymphocyte proliferation in a dose-dependent manner and decreased the percentage of CD4⁺ and CD8⁺ T cell subsets. Interestingly, Exos increased Treg cell populations while parental MSCs did not. Conversely, plasmablast differentiation

was reduced to a similar extent by MSCs, Exos or MPs. IFN- γ priming of MSCs before vesicles isolation did not influence the immunomodulatory function of isolated Exos or MPs. In DTH, we observed a dose-dependent anti-inflammatory effect of MPs and Exos, while in the CIA model, Exos efficiently decreased clinical signs of inflammation. The beneficial effect of Exos was associated with fewer plasmablasts and more Breg-like cells in lymph nodes. **Conclusions:** Both MSCs-derived MPs and Exos exerted an anti-inflammatory role on T and B lymphocytes independently of MSCs priming. However, Exos were more efficient in suppressing inflammation *in vivo*. Our work is the first demonstration of the therapeutic potential of MSCs-derived EVs in inflammatory arthritis.

[J Cell Mol Med.](#) 2018 Mar 4. doi: 10.1111/jcmm.13545. [Epub ahead of print]

Microtubule defects in mesenchymal stromal cells distinguish patients with Progressive Supranuclear Palsy.

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Abstract

Progressive Supranuclear Palsy (PSP) is a rare neurodegenerative disease whose etiopathogenesis remains elusive. The intraneuronal accumulation of hyperphosphorylated Tau, a pivotal protein in regulating microtubules (MT), leads to include PSP into tauopathies. Pathological hallmarks are well known in neural cells but no word yet if PSP-linked dysfunctions occur also in other cell types. We focused on bone marrow mesenchymal stromal cells (MSCs) that have recently gained attention for therapeutic interventions due to their anti-inflammatory, antiapoptotic and trophic properties. Here, we aimed to investigate MSCs biology and to disclose if any disease-linked defect occurs in this non-neuronal compartment. First, we found that cells obtained from patients showed altered morphology and growth. Next, Western blotting analysis unravelled the imbalance in α -tubulin post-translational modifications and in MT stability. Interestingly, MT mass is significantly decreased in patient cells at baseline and differently changes overtime compared to controls, suggesting their inability to efficiently remodel MT cytoskeleton during ageing in culture. Thus, our results provide the first evidence that defects in MT regulation and stability occur and are detectable in a non-neuronal compartment in patients with PSP. We suggest that MSCs could be a novel model system for unravelling cellular processes implicated in this neurodegenerative disorder.

[Dermatol Ther \(Heidelb\).](#) 2018 Mar 2. doi: 10.1007/s13555-018-0229-2. [Epub ahead of print]

Anti-aging Properties of Conditioned Media of Epidermal Progenitor Cells Derived from Mesenchymal Stem Cells.

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Abstract

INTRODUCTION:

Reduced number and activities of epidermal stem cells are related to the features of photoaged skin. It was reported that conditioned media from various stem cell cultures are capable of improving the signs of cutaneous aging. This work was performed to establish epidermal progenitor cells derived from mesenchymal stem cells, and to evaluate the anti-aging efficacy of its conditioned media.

METHODS:

Epidermal progenitor cell culture was established by differentiation from mesenchymal stem cells, and its conditioned medium (EPC-CM) was prepared. Normal human dermal fibroblasts were exposed to hydrogen peroxide and the protective effects of EPC-CM were investigated, monitoring intracellular reactive oxygen species (ROS), cellular defense enzymes, collagen biosynthesis, and mitogen-associated protein kinase (MAPK) signaling. Anti-aging efficacy of cosmetic essence (5% EPC-CM) was evaluated by a clinical test with 25 Korean women aged between 29 and 69.

RESULTS:

Hydrogen peroxide hindered proliferation of fibroblasts and increased the levels of intracellular ROS. Pretreatment of EPC-CM protected fibroblasts from oxidative stress as shown by accelerated proliferation and reduced ROS generation. EPC-CM effectively prevented hydrogen peroxide-induced alterations of the activities, as well as mRNA and protein levels, of antioxidative enzymes, such as superoxide dismutase, catalase, and glutathione peroxidase. Reduced type I collagen biosynthesis and stimulated phosphorylation of MAPK signaling proteins, induced by oxidative damage, were also prevented by EPC-CM. In clinical study, wrinkle, depression, and skin texture were improved by the topical application of a formulation containing 5% EPC-CM within 4 weeks.

CONCLUSION:

Epidermal progenitor cell culture was established, and its conditioned medium was developed for anti-aging therapy. EPC-CM improved signs of skin aging in clinical study, possibly via activation of cellular the defense system, as supported by in vitro results.

[Int J Mol Sci](#). 2018 Feb 27;19(3). pii: E669. doi: 10.3390/ijms19030669.

Three-Dimensional Graphene-RGD Peptide Nanoisland Composites That Enhance the Osteogenesis of Human Adipose-Derived Mesenchymal Stem Cells.

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Abstract

Graphene derivatives have immense potential in stem cell research. Here, we report a three-dimensional graphene/arginine-glycine-aspartic acid (RGD) peptide nanoisland composite effective in guiding the osteogenesis of human adipose-derived mesenchymal stem cells (ADSCs). Amine-modified silica nanoparticles (SiNPs) were uniformly coated onto an indium tin oxide electrode (ITO), followed by graphene oxide (GO) encapsulation and electrochemical deposition of gold nanoparticles. A RGD-

MAP-C peptide, with a triple-branched repeating RGD sequence and a terminal cysteine, was self-assembled onto the gold nanoparticles, generating the final three-dimensional graphene-RGD peptide nanoisland composite. We generated substrates with various gold nanoparticle-RGD peptide cluster densities, and found that the platform with the maximal number of clusters was most suitable for ADSC adhesion and spreading. Remarkably, the same platform was also highly efficient at guiding ADSC osteogenesis compared with other substrates, based on gene expression (alkaline phosphatase (ALP), runt-related transcription factor 2), enzyme activity (ALP), and calcium deposition. ADSCs induced to differentiate into osteoblasts showed higher calcium accumulations after 14-21 days than when grown on typical GO-SiNP complexes, suggesting that the platform can accelerate ADSC osteoblastic differentiation. The results demonstrate that a three-dimensional graphene-RGD peptide nanoisland composite can efficiently derive osteoblasts from mesenchymal stem cells.

[Oncol Rep.](#) 2018 Apr;39(4):2031-2039. doi: 10.3892/or.2018.6272. Epub 2018 Feb 15.

High expression of TRAIL by osteoblastic differentiated dental pulp stem cells affects myeloma cell viability.

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Abstract

Cells from dental tissues have a mesenchymal stem cell (MSC) phenotype, are multipotent and can differentiate into osteoblastic cells, as we have previously found. MSCs, due to their tumor-homing ability, are currently being used as cell-based delivery systems for cancer protein therapeutics, such as the TNF-related apoptosis-inducing ligand (TRAIL). In the present study we revealed that dental pulp stem cells (DPSCs) expressed TRAIL to a greater extent when they were differentiated into the osteoblastic lineage. TRAIL affected the viability of undifferentiated DPSCs, while osteoblastic differentiated DPSCs were not sensitive to TRAIL. The expression trend of TRAIL receptors underwent changes during the osteoblastic differentiation of DPSCs exhibiting low DcR2 and high DR5 levels in the undifferentiated DPSCs and an opposite scenario was presented in the differentiated cells. The sensitivity of the undifferentiated DPSCs to the TRAIL-apoptotic effect was also associated with low levels of intracellular anti-apoptotic proteins, such as c-FLIP, XIAP and the activation of caspase-8 and -3. DPSC-differentiated osteoblasts expressing high TRAIL levels were capable to affect the cell viability of the human myeloma cell line H929, thus representing an effective anticancer therapeutic method.

[Stem Cell Res Ther.](#) 2018 Feb 26;9(1):45. doi: 10.1186/s13287-018-0802-8.

Strategies to improve the therapeutic effects of mesenchymal stromal cells in respiratory diseases.

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Author information

Abstract

Due to their anti-inflammatory, antiapoptotic, antimicrobial, and antifibrotic properties, mesenchymal stromal cells (MSCs) have been considered a promising alternative for treatment of respiratory diseases. Nevertheless, even though MSC administration has been demonstrated to be safe in clinical trials, to date, few studies have shown evidence of MSC efficacy in respiratory diseases. The present review describes strategies to enhance the beneficial effects of MSCs, including preconditioning (under hypoxia, oxidative stress, heat shock, serum deprivation, and exposure to inflammatory biological samples) and genetic manipulation. These strategies can variably promote increases in MSC survival rates, by inducing expression of cytoprotective genes, as well as increase MSC potency by improving secretion of reparative factors. Furthermore, these strategies have been demonstrated to enhance the beneficial effects of MSCs in preclinical lung disease models. However, there is still a long way to go before such strategies can be translated from bench to bedside.