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Injectable Systems for Intra-Articular Delivery of Mesenchymal Stromal Cells for Cartilage Treatment: A Systematic Review of Preclinical and Clinical Evidence.

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Author information

Abstract

Stem cell-based therapy is a promising approach to treat cartilage lesions and clinical benefits have been reported in a number of studies. However, the efficacy of cell injection procedures may be impaired by cell manipulation and damage as well as by cell dissemination to non-target tissues. To overcome such issues, mesenchymal stromal cell (MSC) delivery may be performed using injectable vehicles as containment systems that further provide a favorable cell microenvironment. The aim of this systematic review was to analyze the preclinical and clinical literature on platelet-rich plasma (PRP), hyaluronic acid (HA), and hydrogels for the delivery of MSCs. The systematic literature search was performed using the PubMed and Web of science databases with the following string: "(stem cells injection) AND (platelet rich plasma OR PRP OR platelet concentrate OR biomaterials OR hyaluronic acid OR hydrogels)": 40 studies (19 preclinical and 21 clinical) met the inclusion criteria. This review revealed an increasing interest on the use of injectable agents for MSC delivery. However, while negligible adverse events and promising clinical outcomes were generally reported, the prevalence of low quality studies hinders the possibility to demonstrate the real benefits of using such injectable systems. Specific studies must be designed to clearly demonstrate the added benefits of these systems to deliver MSCs for the treatment of cartilage lesions and osteoarthritis

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Stability enhancement of clinical grade multipotent mesenchymal stromal cell-based products.

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Abstract

BACKGROUND:

Successful delivery of cell-based therapeutics into patients is compromised by their short shelf-life upon release from production facilities due to the living nature of the active component that rapidly loses viability, and therefore its properties. In this context, the use of appropriate additives may contribute to the stabilisation of the cellular component within specifications for a longer time until administration.

RESULTS:

In the present study, we evaluated the effect of different formulations on the stability of viability, identity, and potency of clinical grade multipotent mesenchymal stromal cells in suspension, both electrolyte solution and protein content were found to impact on their shelf-life. Particularly cryopreservation of cells in a Plasmalyte 148 supplemented with 2% (w/v) AlbIX (a yeast-derived recombinant albumin) and 10% (v/v) dimethyl sulfoxide, and final formulation post-thawing in Plasmalyte 148 supplemented with 2% (w/v) AlbIX enabling prolonged stability from 24 h up to 72 h in optimal conditions. Further investigation on the mechanisms of action involved revealed a delay of apoptosis progression into late stage when AlbIX was present.

CONCLUSIONS:

The use of optimal formulations for each cell type of interest is crucial to extend the shelf life of cell-based pharmaceuticals and contribute to solve logistical challenges. We demonstrated that the use of Plasmalyte 148 supplemented with 2% (w/v) AlbIX resulted in superior stability of multipotent mesenchymal stromal cells without affecting their identity and multipotency.

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Ovarian carcinoma-associated mesenchymal stem cells arise from tissue-specific normal stroma.

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Abstract

Carcinoma-associated mesenchymal stem cells (CA-MSCs) are critical stromal progenitor cells within the tumor microenvironment. We previously demonstrated that CA-MSCs differentially express BMP family members, promote tumor cell growth, increase cancer "stemness" and chemotherapy resistance. Here we use RNA sequencing of normal omental MSCs and ovarian CA-MSCs to demonstrate global changes in CA-MSC gene expression. Using these expression profiles, we create a unique predictive algorithm to classify CA-MSCs. Our classifier accurately distinguishes normal omental, ovary and bone marrow MSCs from ovarian cancer CA-MSCs. Suggesting broad applicability, the model correctly classifies pancreatic and endometrial cancer CA-MSCs and distinguishes cancer associated fibroblasts (CAFs) from CA-MSCs. Using this classifier, we definitively demonstrate ovarian CA-MSCs arise from tumor mediated reprograming of local tissue MSCs. While cancer cells alone cannot induce a CA-MSC phenotype, the in vivo ovarian tumor microenvironment (TME) can reprogram omental or ovary MSCs to protumorigenic CA-MSCs (classifier score of >0.96). In vitro studies suggest that both tumor secreted factors and hypoxia are critical to induce the CA-MSC phenotype. Interestingly, while the breast cancer TME can reprogram BM MSCs into CA-MSCs, the ovarian TME cannot, demonstrating for the first time that tumor mediated CA-MSC conversion is tissue and cancer type dependent. Together these findings (1) provide a critical tool to define CA-MSCs and (2) highlight cancer cell influence on distinct normal tissues providing powerful insights into the mechanisms underlying cancer specific metastatic niche formation.

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Silk/Fibroin Microcarriers for Mesenchymal Stem Cell Delivery: Optimization of Cell Seeding by the Design of Experiment.

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Abstract

In this methodological paper, lyophilized fibroin-coated alginate microcarriers (LFAMs) proposed as mesenchymal stem cells (MSCs) delivery systems and optimal MSCs seeding conditions for cell adhesion rate and cell arrangement, was defined by a Design of Experiment (DoE) approach. Cells were co-incubated with microcarriers in a bioreactor for different time intervals and conditions: variable stirring speed, dynamic culture intermittent or continuous, and different volumes of cells-LFAMs loaded in the bioreactor. Intermittent dynamic culture resulted as the most determinant parameter; the volume of LFAMs/cells suspension and the speed used for the dynamic culture contributed as well, whereas time was a less influencing parameter. The optimized seeding conditions were: 98 min of incubation time, 12.3 RPM of speed, and 401.5 µL volume of cells-LFAMs suspension cultured with the intermittent dynamic condition. This DoE predicted protocol was then validated on both human Adipose-derived Stem Cells (hASCs) and human Bone Marrow Stem Cells (hBMSCs), revealing a good cell adhesion rate on the surface of the carriers. In conclusion, microcarriers can be used as cell delivery systems at the target site (by injection or arthroscopic technique), to maintain MSCs and their activity at the injured site for regenerative medicine.

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The Healing Effects of Conditioned Medium Derived from Mesenchymal Stem Cells on Radiation-Induced Skin Wounds in Rats.

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Abstract

Radioactive dermatitis is caused by the exposure of skin and mucous membranes to radiation fields. The pathogenesis of radioactive dermatitis is complex and difficult to cure. Wharton's jelly-derived mesenchymal stem cells (WJ-MSCs) may serve as a promising candidate for the therapy of cutaneous wounds. The aim of this study was to investigate whether a WJ-MSC-derived conditioned medium (MSC-CM) could be used to treat radiation-induced skin wounds in rats using a radiation-induced cutaneous injury model. The present study was designed to examine MSC-CM therapy in the recovery of radiation-induced skin wounds in vitro and in vivo. Firstly, we prepared the MSC-CM and tested the effects of the MSC-CM on human umbilical vein endothelial cell proliferation in vitro. After that, we used a β-ray beam to make skin wounds in rats and tested the effects of MSC-CM on cutaneous wound

healing in vivo. Our results indicated that MSC-CM secreted factors that promoted HUVEC proliferation, regeneration of sebaceous glands, and angiogenesis. Importantly, MSC-CM promoted wound healing in excess of the positive control (epidermal growth factor), with no, or smaller, scar formation. In conclusion, MSC-CM significantly accelerated wound closure and enhanced the wound healing quality. MSC-CM has a beneficial therapeutic effect on radiation-induced cutaneous injury skin in rats and in this way MSC-CM may serve as a basis of a novel cell-free therapeutic approach for radiation dermatitis.

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A Light-Triggered Mesenchymal Stem Cell Delivery System for Photoacoustic Imaging and Chemo-Photothermal Therapy of Triple Negative Breast Cancer.

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Abstract

Targeted therapy is highly challenging and urgently needed for patients diagnosed with triple negative breast cancer (TNBC). Here, a synergistic treatment platform with plasmonic-magnetic hybrid nanoparticle (lipids, doxorubicin (DOX), gold nanorods, iron oxide nanocluster (LDGI))-loaded mesenchymal stem cells (MSCs) for photoacoustic imaging, targeted photothermal therapy, and chemotherapy for TNBC is developed. LDGI can be efficiently taken up into the stem cells with good biocompatibility to maintain the cellular functions. In addition, CXCR4 on the MSCs is upregulated by iron oxide nanoparticles in the LDGI. Importantly, the drug release and photothermal therapy can be simultaneously achieved upon light irradiation. The released drug can enter the cell nucleus and promote cell apoptosis. Interestingly, light irradiation can control the secretion of cellular microvehicles carrying LDGI for targeted treatment. A remarkable in vitro anticancer effect is observed in MDA-MB-231 with near-infrared laser irradiation. In vivo studies show that the MSCs-LDGI has the enhanced migration and penetration abilities in the tumor area via both intratumoral and intravenous injection approaches compared with LDGI. Subsequently, MSCs-LDGI shows the best antitumor efficacy via chemo-photothermal therapy compared to other treatment groups in the TNBC model of nude mice. Thus, MSCs-LDGI multifunctional system represents greatly synergistic potential for cancer treatment.

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c-Fos induces chondrogenic tumor formation in immortalized human mesenchymal progenitor cells.

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Abstract

Mesenchymal progenitor cells (MPCs) have been hypothesized as cells of origin for sarcomas, and c-Fos transcription factor has been showed to act as an oncogene in bone tumors. In this study, we show c-Fos is present in most sarcomas with chondral phenotype, while multiple other genes are related to c-Fos expression pattern. To further define the role of c-Fos in sarcomagenesis, we expressed it in primary human MPCs (hMPCs), immortalized hMPCs and transformed murine MPCs (mMPCs). In immortalized hMPCs, c-Fos expression generated morphological changes, reduced mobility capacity and impaired adipogenic- and osteogenic-differentiation potentials. Remarkably, immortalized hMPCs or mMPCs expressing c-Fos generated tumors harboring a chondrogenic phenotype and morphology. Thus, here we show that c-Fos protein has a key role in sarcomas and that c-Fos expression in immortalized MPCs yields cell transformation and chondrogenic tumor formation.