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Delivery of LNA-antimiR-142-3p by Mesenchymal Stem Cells-Derived Exosomes to Breast Cancer Stem Cells Reduces Tumorigenicity.

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Abstract

Exosomes, nano-sized cell-derived vesicles, have been employed as non-synthetic carriers of various pharmaceutics in numerous studies. As higher expression levels of miR-142-3p and miR-150 in breast cancer stem cells (BCSCs) are associated with their clonogenic and tumorigenic capabilities, the present study aims to exploit the mesenchymal stem cells-derived exosomes (MSCs-Exo) to deliver LNA-antimiR-142-3p into MCF7-derived cancer stem-like cells to suppress expression levels of miR-142-3p and miR-150 in order to reduce clonogenicity and tumorigenicity. Our results indicated that the MSCs-Exo can efficiently deliver the LNA-antimiR-142-3p to breast cancer stem-like cells to reduce the miR-142-3p and miR-150 expression levels. Furthermore, the inhibition of the oncomiRs with the delivery of LNA-antimiR-142-3p resulted in a significant reduction of clone-formation and tumor-initiating abilities of the MCF7-derived cancer stem-like cells. In conclusion, we showed that MSCs-derived exosomes could be used as a feasible nanovehicles to deliver RNA-based therapeutics into BCSCs to improve the cancer treatment. HIGHLIGHTS: Exosomes secreted by bone marrow-derived mesenchymal stem cells efficiently transfer the LNA-antimiR-142-3p to breast cancer stem cells. Exosomes-mediated delivery of LNA-antimiR-142-3p to the breast cancer stem cells leads to downregulation of miR-142-3p and miR-150 and the overexpression of target genes. Delivery of LNA-antimiR-142-3p by the exosomes reduces the colony formation capability of breast cancer stem cells in vitro. Inhibition of miR-142-3p and miR-150 by the LNA-antimiR-142-3p loaded exosomes reduces the tumorigenicity of breast cancer stem cells in vivo.

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Biocompatibility assessment of sub-5 nm silica-coated superparamagnetic iron oxide nanoparticles in human stem cells and in mice for potential application in nanomedicine.

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Abstract

Ultrasmall superparamagnetic iron oxide nanoparticles with a size <5 nm are emerging nanomaterials for their excellent biocompatibility, chemical stability, and tunable surface modifications. The applications explored include dual-modal or multi-modal imaging, drug delivery, theranostics and, more

recently, magnetic resonance angiography. Good biocompatibility and biosafety are regarded as the preliminary requirements for their biomedical applications and further exploration in this field is still required. We previously synthesized and characterized ultrafine (average core size of 3 nm) silica-coated superparamagnetic iron oxide fluorescent nanoparticles, named sub-5 SIO-Fl, uniform in size, shape, chemical properties and composition. The cellular uptake and in vitro biocompatibility of the as-synthesized nanoparticles were demonstrated in a human colon cancer cellular model. Here, we investigated the biocompatibility of sub-5 SIO-Fl nanoparticles in human Amniotic Mesenchymal Stromal/Stem Cells (hAMSCs). Kinetic analysis of cellular uptake showed a quick nanoparticle internalization in the first hour, increasing over time and after long exposure (48 h), the uptake rate gradually slowed down. We demonstrated that after internalization, sub-5 SIO-Fl nanoparticles neither affect hAMSC growth, viability, morphology, cytoskeletal organization, cell cycle progression, immunophenotype, and the expression of pro-angiogenic and immunoregulatory paracrine factors nor the osteogenic and myogenic differentiation markers. Furthermore, sub-5 SIO-Fl nanoparticles were intravenously injected into mice to investigate the in vivo biodistribution and toxicity profile for a time period of 7 weeks. Our findings showed an immediate transient accumulation of nanoparticles in the kidney, followed by the liver and lungs, where iron contents increased over a 7-week period. Histopathology, hematology, serum pro-inflammatory response, body weight and mortality studies demonstrated a short- and long-term biocompatibility and biosafety profile with no apparent acute and chronic toxicity caused by these nanoparticles in mice. Overall, these results suggest the feasibility of using sub-5 SIO-Fl nanoparticles as a promising agent for stem cell magnetic targeting as well as for diagnostic and therapeutic applications in oncology.

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Quantitative Tracking Tumor Suppression Efficiency of Human Umbilical Cord-Derived Mesenchymal Stem Cells by Bioluminescence Imaging in Mice Hepatoma Model.

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Abstract

BACKGROUND AND OBJECTIVES:

Tracking of the tumor progression by MSCs-based therapy is being increasingly important in evaluating relative therapy effectively. Herein, Bioluminescence imaging (BLI) technology was used to dynamically and quantitatively track the hepatocellular carcinoma suppressive effects by human umbilical cord mesenchymal stem cells (UC-MSCs).

METHODS AND RESULTS:

The stem cells present typical phenotypic characteristics and differentiation ability by morphology and flow cytometry analysis of marker expression. Then, the growth inhibition effect of conditioned medium and UC-MSC on H7402 cells was studied. It is found both the conditioned medium and UC-MSC can

effectively decrease the proliferation of H7402 cells compared with the control group. Meanwhile, the relative migration of UC-MSC to H7402 is also increased through the transwell migration assay. In addition, a mice hepatoma tumor model was built by H7402 cells which can express a pLenti-6.3/DEST-CMV-luciferase 2-mKate2 gene. The effect of stem cells on growth inhibition of tumor in a mice transplantation model was dynamically monitored by bioluminescence imaging within 5 weeks. It has shown the bioluminescence signal intensity of the tumor model was significantly higher than that of the UC-MSC co-acting tumor model, indicating that the inhibition of UC-MSC on liver cancer resulted in low expression of bioluminescent signals.

CONCLUSIONS:

The microenvironment of UC-MSCs can effectively inhibit the growth of liver cancer cells, and this therapeutic effect can be dynamically and quantitatively monitored in vivo by BLI. This is of great significance for the imaging research and application of stem cells in anticancer therapy.

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Protective Effect of Human Mesenchymal Stem Cells on the Survival of Pancreatic Islets.

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Abstract

BACKGROUND AND OBJECTIVES:

Transplantation of pancreatic islets is an intriguing new therapeutic option to face the worldwide spread problem of Type-I diabetes. Currently, its clinical use is limited by several problems, mainly based on the high number of islets required to restore normoglycaemia and by the low survival of the transplanted tissue. A promising attempt to overcome the limits to such an approach was represented by the use of Mesenchymal Stem Cells (MSC). Despite the encouraging results obtained with murine-derived MSC, little is still known about their protective mechanisms. The aim of the present study was to verify the effectiveness, (besides murine MSC), of clinically relevant human-derived MSC (hMSC) on protecting pancreatic islets, thus also shedding light on the putative differences between MSC of different origin.

METHODS AND RESULTS:

Threefold kinds of co-cultures were therefore in vitro set up (direct, indirect and mixed), to analyze the hMSC effect on pancreatic islet survival and function and to study the putative mechanisms involved. Although in a different way with respect to murine MSC, also human derived cells demonstrated to be effective on protecting pancreatic islet survival. This effect could be due to the release of some trophic factors, such as VEGF and Il-6, and by the reduction of inflammatory cytokine TNF-α.

CONCLUSIONS:

Therefore, hMSC confirmed their great clinical potential to improve the feasibility of pancreatic islet transplantation therapy against diabetes.

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Autologous Microfragmented Adipose Tissue Reduces the Catabolic and Fibrosis Response in an In Vitro Model of Tendon Cell Inflammation.

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Abstract

BACKGROUND:

Mesenchymal stem cells (MSCs) emerged as a promising therapy for tendon pathologies. Microfragmented adipose tissue (*μ*FAT) represents a convenient autologous product for the application of MSC-based therapies in the clinical setting. In the present study, the ability of *μ*FAT to counteract inflammatory processes induced by IL-1*β* on human tendon cells (TCs) was evaluated.

METHODS:

Cell viability and proliferation were evaluated after 48 hours of transwell coculture of TCs and autologous *μ*FAT in the presence or absence of IL-1*β*. Gene expression of scleraxis, collagen type I and type III, metalloproteinases-1 and -3, and cyclooxygenase-2 was evaluated by real-time RT-PCR. The content of VEGF, IL-1Ra, TNF*α*, and IL-6 was evaluated by ELISA.

RESULTS:

IL-1*β*-treated TCs showed augmented collagen type III, metalloproteases, and cyclooxygenase-2 expression. *μ*FAT was able to reduce the expression of collagen type III and metalloproteases-1 in a significant manner, and at the same time, it enhanced the production of VEGF, IL-1Ra, and IL-6.

CONCLUSIONS:

In this in vitro model of tendon cell inflammation, the paracrine action of *μ*FAT, exerted by anti-inflammatory molecules and growth factors, was able to inhibit the expression of fibrosis and catabolic markers. Then, these results suggest that the application of *μ*FAT may represent an effective conservative or adjuvant therapy for the treatment of tendon disorders.

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Novel Cryopreservation Approach Providing Off-the-Shelf Availability of Human Multipotent Mesenchymal Stromal Cells for Clinical Applications.

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Abstract

Cryopreservation is the only established method to provide long-term storage and fast availability of cellular product for therapeutic applications. The overwhelming majority of cryopreservation media contain toxic concentrations of dimethyl sulfoxide (DMSO) limiting the possibility for the direct administration of cryopreserved cells to the patients. Here, we propose a novel approach for nontoxic xeno-free cryopreservation of human multipotent mesenchymal stromal cells (MSCs) aimed at ensuring high viability, ready-to-use availability, and localized delivery of the cell-based graft into damaged tissues. For MSC cryopreservation, we applied sucrose pretreatment procedure and xeno-free cryoprotective medium containing human platelet-poor blood plasma (PPP), sucrose, and nontoxic concentration of DMSO. Using the combination of PPP, 0.2 M sucrose, and 1% DMSO, the recovery rate of cryopreserved MSCs reached 73% of the values obtained for noncryopreserved cells. Moreover, the presence of PPP in the cryoprotective medium provided the possibility to create a ready-to-use 3D hydrogel for the localized delivery and additional support of MSCs *in vivo*. In a proof-of-concept study, we assessed the regenerative capacity of cryopreserved MSCs in a full-thickness wound model in mice. The positive impact of MSCs within 3D gel on wound healing rates was confirmed by morphometric and histological examinations. Our results demonstrate the possibility to apply cryopreserved cells immediately after thawing using a cryoprotective medium as the vehicle solution.

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An Enzyme-free Method for Isolation and Expansion of Human Adipose-derived Mesenchymal Stem Cells.

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Abstract

Mesenchymal stem cells (MSCs) are a population of multipotent cells that can be isolated from various adult and fetal tissues, including adipose tissue. As a clinically relevant cell type, optimal methods are needed to isolate and expand these cells in vitro. Most methods to isolate adipose-derived MSCs (ADSCs) rely on harsh enzymes, such as collagenase, to digest the adipose tissue. However, while effective at breaking down the adipose tissue and yielding a high ADSC recovery, these enzymes are expensive and can have detrimental effect on the ADSCs - including the risks of using xenogeneic components in clinical applications. This protocol details a method to isolate ADSCs from fresh lipoaspirate and abdominoplasty samples without enzymes. Briefly, this method relies on mechanical disassociation of any bulk tissue followed by an explant-type culture system. The ADSCs are permitted to migrate out of tissue and onto the tissue culture plate, after which the ADSCs can be cultured and expanded in vitro for any number of research and/or clinical application

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Mesenchymal Stem Cells Attract Endothelial Progenitor Cells via a Positive Feedback Loop between CXCR2 and CXCR4.

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Abstract

Mesenchymal stem cells (MSCs) can attract host endothelial progenitor cells (EPCs) to promote vascularization in tissue-engineered constructs (TECs). Nevertheless, the underlying mechanism remains vague. This study is aimed at investigating the roles of CXCR2 and CXCR4 in the EPC migration towards MSCs. *In vitro*, Transwell assays were performed to evaluate the migration of EPCs towards MSCs. Antagonists and shRNAs targeting CXCR2, CXCR4, and JAK/STAT3 were applied for the signaling blockade. Western blot and RT-PCR were conducted to analyze the molecular events in EPCs. *In vivo*, TECs were constructed and subcutaneously implanted into GFP^+ transgenic mice. Signaling inhibitors were injected in an orientated manner into TECs. Recruitment of host $CD34^+$ cells was evaluated by immunofluorescence. Eventually, we demonstrated that CXCR2 and CXCR4 were both highly expressed in migrated EPCs and indispensable for MSC-induced EPC migration. CXCR2 and CXCR4 strongly correlated with each other in the way that the expression of CXCR2 and CXCR2-mediated migration depends on the activity of CXCR4 and vice versa. Further studies documented that both of CXCR2 and CXCR4 activated STAT3 signaling, which in turn regulated the expression of CXCR2 and CXCR4, as well as cell migration. In summary, we firstly introduced a reciprocal crosstalk between CXCR2 and CXCR4 in the context of EPC migration. This feedback loop plays critical roles in the migration of EPCs towards MSCs.