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Engineered Mesenchymal Stem Cell/Nanomedicine Spheroid as an Active Drug Delivery Platform for Combinational Glioblastoma Therapy.

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Abstract

Mesenchymal stem cell (MSC) has been increasingly applied to cancer therapy because of its tumor-tropic capability. However, short retention at target tissue and limited payload option hinder the progress of MSC-based cancer therapy. Herein, we proposed a hybrid spheroid/nanomedicine system, comprising MSC spheroid entrapping drug-loaded nanocomposite, to address these limitations. Spheroid formulation enhanced MSC's tumor tropism and facilitated loading of different types of therapeutic payloads. This system acted as an active drug delivery platform seeking and specifically targeting glioblastoma cells. It enabled effective delivery of combinational protein and chemotherapeutic drugs by engineered MSC and nanocomposite, respectively. In an in vivo migration model, the hybrid spheroid showed higher nanocomposite retention in the tumor tissue compared with the single MSC approach, leading to enhanced tumor inhibition in a heterotopic glioblastoma murine model. Taken together, this system integrates the merits of cell- and nanoparticle- mediated drug delivery with the tumor-homing characteristics of MSC to advance targeted combinational cancer therapy.

Hematol Transfus Cell Ther. 2019 Jan-Mar;41(1):7-16. doi: 10.1016/j.htct.2018.05.001. Epub 2018 Jun 19.

Standardization and quality assessment for clinical grade mesenchymal stem cells from human adipose tissue.

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Abstract

BACKGROUND:

Mesenchymal stem cells have immense potential in stem cell-based therapies, however there is a pre-requisite to develop a curative cell dose. Adipose tissue-derived mesenchymal stem cells are promising mainly due to their potential abundance, immunomodulatory effect and remarkable differentiation potential. Nevertheless, senescence may develop during their *in vitro* expansion due to the incidence of genetic instability. Hence, it is important to attain an ideal balance between mesenchymal stem cell growth, quality and genetic integrity before their clinical use.

METHODS:

Stromal vascular fraction was obtained from omentum tissue of patients undergoing liposuction procedures for morbid obesity. This study standardized a closed system protocol which can be utilized

for clinical grade stem cell derivation. Stages of cell growth and characterization of human adipose tissue-derived mesenchymal stem cells were also assessed along with the chromosomal stability in these *in vitro* cultures.

RESULTS:

Human adipose tissue-derived mesenchymal stem cells maintained their spindle-shaped morphology and were able to proliferate and renew, confirming their suitability for *in vitro* cultivation and generate clinical grade mesenchymal stem cells. Immunophenotyping indicates that the cells expressed cluster of differentiation (CD)73/CD90/CD105, mesenchymal stem-cell markers, while lacked CD34/CD45/ Human Leukocyte antigen-antigen D related (HLA-DR) expression (hematopoietic cell markers). A cell cycle study demonstrated growth kinetics under *in vitro* culture conditions. Human adipose tissue derived mesenchymal stem cells expressed normal cell karyotype by chromosomal G-banding indicating their genetic stability at Passage 5. Mesenchymal stem cells also demonstrated trilineage differentiation.

CONCLUSIONS:

Availability of adipose tissue in abundance is a major advantage for clinical applications. Furthermore, detailed characterization of human adipose tissue-derived mesenchymal stem cells, their genomic stability and differentiation potential from stromal vascular fraction of human adipose tissue would help assist in tissue regeneration and repair.

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Genome-wide DNA-methylation profiles in human bone marrow mesenchymal stem cells on titanium surfaces.

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Abstract

The characteristics of titanium (Ti) have been shown to influence dental implant fixation. Treatment of surfaces using the sandblasted, large-grit, acid-etched (SLA) method is widely used to provide effective osseointegration. However, the DNA methylation-associated mechanism by which SLA surface treatment affects osseointegration of human bone marrow mesenchymal stem cells (hBMSCs) remains elusive. Genome-wide methylation profiling of hBMSCs on SLA-treated and machined smooth Ti was performed using Illumina Infinium Methylation EPIC BeadChip at day 7 of osteogenic induction. In total, 2,846 CpG sites were differentially methylated in the SLA group compared with the machined group. Of these sites, 1,651 (covering 1,066 genes) were significantly hypermethylated and 1,195 (covering 775 genes) were significantly hypomethylated. Thirty significant enrichment pathways were observed, with Wnt signaling being the most significant. mRNA expression was identified by microarray and combined with DNA-methylation profiles. Thirty-seven genes displayed negative association between mRNA expression and DNA-methylation level, with the osteogenesis-related genes insulin-like growth factor 2 (IGF2) and carboxypeptidase X, M14 Family Member 2 (CPXM2) showing significant up-regulation and down-regulation, respectively. In summary, our results demonstrate differences between SLA-treated

and machined surfaces in their effects on genome-wide DNA methylation and enrichment of osteogenic pathways in hBMSCs. We provide novel insights into genes and pathways affected by SLA treatment in hBMSCs at the molecular level.

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Mesenchymal stem cell basic research and applications in dog medicine.

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Abstract

The stem cells, owing to their special characteristics like self-renewal, multiplication, homing, immunomodulation, anti-inflammatory, and dedifferentiation are considered to carry an "all-in-one-solution" for diverse clinical problems. However, the limited understanding of cellular physiology currently limits their definitive therapeutic use. Among various stem cell types, currently mesenchymal stem cells are extensively studied for dog clinical applications owing to their readily available sources, easy harvesting, and ability to differentiate both into mesodermal, as well as extramesodermal tissues. The isolated, culture expanded, and characterized cells have been applied both at preclinical as well as clinical settings in dogs with variable but mostly positive results. The results, though positive, are currently inconclusive and demands further intensive research on the properties and their dependence on the applications. Further, numerous clinical conditions of dog resemble to that of human counterparts and thus, if proved rewarding in the former may act as basis of therapy for the latter. The current review throws some light on dog mesenchymal stem cell properties and their potential therapeutic applications.

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Periosteum-derived mesenchymal progenitor cells in engineered implants promote fracture healing in a critical-size defect rat model.

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Abstract

An attractive alternative to bone autografts is the use of autologous mesenchymal progenitor cells (MSCs) in combination with biomaterials. We compared the therapeutic potential of different sources of mesenchymal stem cells in combination with biomaterials in a bone nonunion model. A critical-size defect was created in Sprague-Dawley rats. Animals were divided into six groups, depending on the treatment to be applied: bone defect was left empty (CTL); treated with live bone allograft (LBA); hrBMP-2 in collagen scaffold (CS^{BMP2}); acellular polycaprolactone scaffold (PCL group); PCL scaffold containing periosteum-derived MSCs (PCL^{PMSCs}) and PCL containing bone marrow-derived MSCs (PCL^{BMSCs}). To facilitate cell tracking, both MSCs and bone graft were isolated from GFP-transgenic

rats. CTL group did not show any signs of healing during the radiological follow-up (n=6). In the LBA group, all the animals showed bone bridging (n=6) while in the CS^{BMP2} group, 4 out of 6 animals demonstrated healing. In PCL and PCL^{PMSCs} groups, a reduced number of animals showed radiological healing, while no healing was detected in the PCL^{BMSCs} group. Using micro-computed tomography, the bone volume filling the defect was quantified, showing significant new bone formation in the LBA, CS^{BMP2} and PCL^{PMSCs} groups when compared with the CTL group. At 10 weeks, GFP positive cells were detected only in the LBA group and restricted to the outer cortical bone in close contact with the periosteum. Tracking of cellular implants demonstrated significant survival of the PMSCs when compared with BMSCs. In conclusion, PMSCs improve bone regeneration being suitable for mimetic autograft design.

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Controlled Nanoscale Topographies for Osteogenic Differentiation of Mesenchymal Stem Cells.

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Abstract

Nanotopography with length scales of the order of extracellular matrix elements offers the possibility of regulating cell behavior. Investigation of the impact of nanotopography on cell response has been limited by the inability to precisely control geometries, especially at high spatial resolutions and across practically large areas. In this paper, we demonstrate well-controlled and periodic nanopillar arrays of silicon and investigate their impact on osteogenic differentiation of human mesenchymal stem cells (hMSCs). Silicon nanopillar arrays with critical dimensions in the range of 40-200 nm, exhibiting standard deviations below 15% across full wafers, were realized using the self-assembly of block copolymer colloids. Immunofluorescence and quantitative polymerase chain reaction measurements reveal clear dependence of osteogenic differentiation of hMSCs on the diameter and periodicity of the arrays. Further, the differentiation of hMSCs was found to be dependent on the age of the donor. While osteoblastic differentiation was found to be promoted by the pillars with larger diameters and heights independent of donor age, they were found to be different for different spacings. Pillar arrays with smaller pitch promoted differentiation from a young donor, while a larger spacing promoted those of an old donor. These findings can contribute for the development of personalized treatments of bone diseases, namely, novel implant nanostructuring depending on patient age.

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Multifunctional nanoparticles for intracellular drug delivery and photoacoustic imaging of mesenchymal stem cells.

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Abstract

Strategies that control the differentiation of mesenchymal stem cells (MSC) and enable image-guided cell implantation and longitudinal monitoring could advance MSC-based therapies for bone defects and injuries. Here we demonstrate a multifunctional nanoparticle system that delivers resveratrol (RESV) intracellularly to improve osteogenesis and enables photoacoustic imaging of MSCs. RESV-loaded nanoparticles (RESV-NPs), formulated from poly (lactic-co-glycolic) acid and iron oxide, enhanced the stability of RESV by 18-fold and served as photoacoustic tomography (PAT) contrast for MSCs. Pre-loading MSCs with RESV-NP upregulated RUNX2 expression with a resultant increase in mineralization by 27% and 45% compared to supplementation with RESV-NP and free RESV, respectively, in 2-dimensional cultures. When grown in polyethylene glycol-based hydrogels, MSCs pre-loaded with RESV-NPs increased the overall level and homogeneity of mineralization compared to those supplemented with free RESV or RESV-NP. The PAT detected RESV-NP-loaded MSCs with a resolution of 1500 cells/μL, which ensured imaging of MSCs upon encapsulation in a PEG-based hydrogel and implantation within the rodent cranium. Significantly, RESV-NP-loaded MSCs in hydrogels did not show PAT signal dilution over time or a reduction in signal upon osteogenic differentiation. This multifunctional NP platform has the potential to advance translation of stem cell-based therapies, by improving stem cell function and consistency via intracellular drug delivery, and enabling the use of a promising emerging technology to monitor cells in a clinically relevant manner.

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Effect of adipose-derived mesenchymal stem cells on hepatocellular carcinoma: *In vitro*inhibition of carcinogenesis.

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Abstract

AIM:

To investigate the effect of adipose-derived mesenchymal stem cells (ADMSCs) and their conditioned media (CM) on hepatocellular carcinoma (HCC) cell tumorigenesis.

METHODS:

The proliferation rate of HepG2 and PLC-PRF-5 HCC cancer cells was measured using the trypan blue exclusion method and confirmed using the cell-counting kit 8 (commonly known as CCK-8) assay. Apoptosis was detected by flow cytometry using annexin V-FITC. Protein and mRNA expression was quantified by ELISA and real time PCR, respectively. Migration and invasion rates were performed by Transwell migration and invasion assays. Wound healing was examined to confirm the data obtained from the migration assays.

RESULTS:

Our data demonstrated that when co-culturing HCC cell lines with ADMSCs or treating them with ADMSC CM, the HCC cell proliferation rate was significantly inhibited and the apoptosis rate increased.

The decreased proliferation rate was accompanied by an upregulation of P53 and Retinoblastoma mRNA and a downregulation of c-Myc and hTERT mRNA levels. More notably, ADMSCs and their CM suppressed the expression of the two important markers of HCC carcinogenicity, alpha-fetoprotein and Des-gamma-carboxyprothrombin. In addition, the migration and invasion levels of HepG2 and PLC-PRF-5 cells significantly decreased, potentially through increased expression of the tissue inhibitor metalloproteinases TIMP-1, TIMP-2 and TIMP-3.

CONCLUSION:

These findings shed new light on a protective and therapeutic role for ADMSCs and their CM in controlling HCC invasiveness and carcinogenesis.