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Mesenchymal Stem Cells Mediated Drug Delivery in Tumor-Targeted Therapy

Mengying Xie[1], Lei Tao[2], Ziqi Zhang[1], Wei Wang[1]
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- PMID: 32819256

- DOI: 10.2174/1567201817999200819140912

Abstract

Mesenchymal stem cells (MSCs) possess unique properties that make them potential carriers for cancer therapy. MSCs have been documented to have low immunogenicity, positive safety in clinical trials, and the ability to selectively homing to inflammation and tumor sites. Thisreview aims to introduce tumor tropism mechanism and effects of MSCs on tumor cells, and give an overview of MSCs in delivering gene therapeutic agents, oncolytic viruses and chemotherapeutics, as well as the application of MSCs-derived exosomes in tumor-targeted therapy.

J Cell Mol Med

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Human amniotic mesenchymal stem cells inhibit hepatocellular carcinoma in tumour-bearing mice

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- PMID: 32798252

- DOI: 10.1111/jcmm.15668

Abstract

Hepatocellular carcinoma (HCC) is the third leading cause of the cancer-related death in the world. Human amniotic mesenchymal stem cells (hAMSCs) have been characterized with a pluripotency, low immunogenicity and no tumorigenicity. Especially, the immunosuppressive and anti-inflammatory effects of hAMSCs make them suitable for treating HCC. Here, we reported that hAMSCs administrated by intravenous injection significantly inhibited HCC through suppressing cell proliferation and inducing cell apoptosis in tumour-bearing mice with Hepg2 cells. Cell tracking experiments with GFP-labelled hAMSCs showed that the stem cells possessed the ability of migrating to the tumorigenic sites for suppressing tumour growth. Importantly, both hAMSCs and the conditional media (hAMSC-CM) have the similar antitumour effects in vitro, suggesting that hAMSCs-derived cytokines might be involved in their antitumour effects. Antibody array assay showed that hAMSCs highly expressed dickkopf-3 (DKK-3), dickkopf-1 (DKK-1) and insulin-like growth factor-binding protein 3 (IGFBP-3). Furthermore, the antitumour effects of hAMSCs were further confirmed by applications of the antibodies or the specific siRNAs of DKK-3, DKK-1 and IGFBP-3 in vitro. Mechanically, hAMSCs-derived DKK-3, DKK-1 and IGFBP-3 markedly inhibited cell proliferation and promoted apoptosis of Hepg2 cells through suppressing the Wnt/β-catenin signalling pathway and IGF-1R-mediated PI3K/AKT signalling pathway, respectively. Taken together, our study demonstrated that hAMSCs possess significant antitumour effects in vivo and in vitro and might provide a novel strategy for HCC treatment clinically.

Front Cell Dev Biol

. 2020 Jul 22;8:619.
doi: 10.3389/fcell.2020.00619. eCollection 2020.

The Application of MSCs-Derived Extracellular Vesicles in Bone

Disorders: Novel Cell-Free Therapeutic Strategy

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- PMID: 32793590
- PMCID: PMC7387669
- DOI: 10.3389/fcell.2020.00619

Free PMC article

Abstract

Bone is crucial for supporting the body, protecting other organs, providing minerals, and secreting hormone to regulate other organ's function. Bone disorders result in pain and disability, severely affecting human health, reducing the quality of life and increasing costs to society. With the rapid increase in the aging population worldwide, bone disorders have become one major disease. As a result, efficacious therapies of bone disorders have become the focus of attention worldwide. Mesenchymal stem cells (MSCs) have been widely explored as a new therapeutic method for numerous diseases. Recent evidence suggests that the therapeutic effects of MSCs are mainly mediated by their extracellular vesicles (EV). MSCs-derived extracellular vesicles (MSCs-EV) is indicated as a novel cell-free alternative to cell therapy with MSCs in regenerative medicine. Here, we review the current knowledge of EV and highlight the application studies of MSCs-EV in bone disorders by focusing on osteoarthritis (OA), rheumatoid arthritis (RA), osteoporosis (OP), and bone fracture. Moreover, we discuss the key issues and perspectives of MSCs-EV as a clinical therapeutic strategy for bone diseases.

Geroscience
.
. 2020 Aug 13.
doi: 10.1007/s11357-020-00250-9. Online ahead of print.

Ageing human bone marrow mesenchymal stem cells have depleted

NAD(P)H and distinct multispectral autofluorescence

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- PMID: 32789662

- DOI: 10.1007/s11357-020-00250-9

Abstract

Stem cell exhaustion plays a major role in the ageing of different tissues. Similarly, in vitro cell ageing during expansion prior to their use in regenerative medicine can severely compromise stem cell quality through progressive declines in differentiation and growth capacity. We utilized non-destructive multispectral assessment of native cell autofluorescence to investigate the metabolic mechanisms of in vitro mesenchymal stem cell (MSC) ageing in human bone marrow MSCs over serial passages (P2-P10). The spectral signals for NAD(P)H, flavins and protein-bound NAD(P)H were successfully isolated using Robust Dependent Component Analysis (RoDECA). NAD(P)H decreased over the course of hMSC ageing in absolute terms as well as relative to flavins (optical redox ratio). Relative changes in other fluorophore levels (flavins, protein-bound NAD(P)H) suggested that this reduction was due to nicotinamide adenine dinucleotide depletion rather than a metabolic shift from glycolysis to oxidative phosphorylation. Using multispectral features, which are determined without cell fixation or fluorescent labelling, we developed and externally validated a reliable, linear model which could accurately categorize the age of culture-expanded hMSCs. The largest shift in spectral characteristics occurs early in hMSC ageing. These findings demonstrate the feasibility of applying multispectral technology for the non-invasive monitoring of MSC health in vitro.

Biochem Biophys Res Commun

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. 2020 Aug 9;S0006-291X(20)31388-7.
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Bone progeria diminished the therapeutic effects of bone marrow

mesenchymal stem cells on retinal degeneration

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- PMID: 32788069

- DOI: 10.1016/j.bbrc.2020.07.007

Free article

Abstract

Senescence is closely related to the occurrence of retinal degeneration. Recent studies have shown that bone marrow mesenchymal stem cells (BMMSCs) have significant therapeutic effects on retinal degeneration, While BMMSCs suffer from functional decline in bone aging. Whether senescence affects BMMSCs therapy on retinal degeneration remains unknown. Here, we applied the previously established bone progeria animal model, the senescence-accelerated mice-prone 6 (SAMP6) strain, and surprisingly discovered that SAMP6 mice demonstrated retinal degeneration at 6 months old. Furthermore, BMMSCs derived from SAMP6 mice failed to prevent MNU-induced retinal degeneration in vivo. As expected, BMMSCs from SAMP6 mice exhibited impairment in the differentiation capacities, compared to those from the age-matched senescence-accelerated mice-resistant 1 (SAMR1) strain. Moreover, BMMSCs from SAMR1 mice counteracted MNU-induced retinal degeneration, with increased expression of the retina survival hallmark, N-myc downstream regulated gene 2 (NDRG2). Taken together, these findings reveal that bone progeria diminished the therapeutic effects of BMMSC on retinal degeneration.

Eur J Pharm Biopharm

. 2020 Aug 9;S0939-6411(20)30240-X.
doi: 10.1016/j.ejpb.2020.08.003. Online ahead of print.

GMP-compliant sponge-like dressing containing MSC lyo-secretome:

proteomic network of healing in a murine wound model

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- PMID: 32784044

- DOI: 10.1016/j.ejpb.2020.08.003

Abstract

Chronic wounds account for 3% of total healthcare expenditure of developed countries; thus, innovative therapies, including Mesenchymal Stem Cells (MSCs) end their exosomes are increasingly considered, even if the activity depends on the whole secretome, made of both soluble proteins and extracellular vesicles. In this work, we prove for the first time the in vivo activity of the whole secretome formulated in a sponge-like alginate wound dressing to obtain the controlled release of bioactive substances. The product has been prepared in a public GMP-compliant facility by a scalable process; based on the murine model, treated wounds healed faster than controls without complications or infections. The treatment induced a higher acute inflammatory process in a short time and sustained the proliferative phase by accelerating fibroblast migration, granulation tissue formation, neovascularization and collagen deposition. The efficacy was substantially supported by the agreement between histological and proteomic findings. In addition to functional modules related to proteolysis, complement and coagulation cascades, protein folding and ECM remodeling, in treated skin, emerged the role of specific wound healing related proteins, including Tenascin (Tnc), Decorin (Dcn) and Epidermal growth factor receptor (EGFR). Of note, Decorin and Tenascin were also components of secretome, and network analysis suggests a potential role in regulating EGFR. Although further experiments will be necessary to characterize better the molecular keys induced by treatment, overall, our results confirm the whole secretome efficacy as novel "cell-free therapy". Also, sponge-like topical dressing containing the whole secretome, GMP- compliant and "ready-off-the-shelf", may represent a relevant point to facilitate its translation into the clinic.

Biogerontology

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doi: 10.1007/s10522-020-09893-9. Online ahead of print.

Multiparameter flow cytometric detection and quantification of senescent cells in vitro

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- PMID: 32776262

- DOI: 10.1007/s10522-020-09893-9

Abstract

It has been over half a century since cellular senescence was first noted and characterized, and yet no consensus senescent marker has been reliably established. This challenge is compounded by the complexity and heterogenic phenotypes of senescent cells. This necessitates the use of multiple biomarkers to confidently characterise senescent cells. Despite cytochemical staining of senescence associated-beta-galactosidase being a single marker approach, as well as being time and labour-intensive, it remains the most popular detection method. We have developed an alternative flow cytometry-based method that simultaneously quantifies multiple senescence markers at a single-cell resolution. In this study, we applied this assay to the quantification of both replicative and induced senescent primary cells. Using this assay, we were able to quantify the activity level of SA β-galactosidase, the expression level of $p16^{INK4a}$ and γH2AX in these cell populations. Our results show this flow cytometric approach to be sensitive, robust, and consistent in discriminating senescent cells in different cell senescence models. A strong positive correlation between these commonly- used senescence markers was demonstrated. The method described in this paper can easily be scaled up to accommodate high-throughput screening of senescent cells in applications such as therapeutic cell preparation, and in therapy-induced senescence following cancer treatment.

Heliyon

. 2020 Aug 1;6(8):e04582.
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Using iron sucrose-labeled adipose-derived mesenchymal stem cells in 1.5

and 3 T MRI tracking: An *in vitro* study

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- PMID: 32775748

- PMCID: PMC7398940

- DOI: 10.1016/j.heliyon.2020.e04582

Free PMC article

Abstract

Objectives: The objective of this study was to investigate iron sucrose labeling in mesenchymal stem cell (MSCs) tracking.

Background: Adipose-derived mesenchymal stem cell-based therapy is a promising strategy for promoting musculoskeletal repair.

Methods: Iron sucrose-labeled adipose-derived mesenchymal stem cells (IS-labeled ASCs) were tracked using T2-and T2∗-weighted sequences by 1.5 and 3 T MRI in an *in vitro* model. ASCs were isolated from cosmetic liposuction specimens. ASCs from passages 4-6 were labeled with iron sucrose (Venofer®) which was added to the cell culture medium. Pre- and post-iron sucrose labeled ASCs were evaluated for cell surface immunophenotypes. Cell viability as well as chondrogenic, adipogenic and osteogenic differentiation of IS-labeled-ASCs were evaluated. The IS-labeled ASCs were titrated into microtubes at 1×10^3, 1×10^4, 1×10^5 and 1×10^6 cells/ml/microtube and their intensities were determined by 1.5 and 3T MRI using T2-and T2∗-weighted sequences.

Results: The expression markers of IS-labeled ASCs from flow cytometry were equivalent to control. The mean cell viability was 97.73 ± 2.06%. Cell differentiations of IS-labeled ASCs were confirmed in each lineage using specific staining solutions. T2∗-weighted sequences (T2∗) were able to detect iron sucrose labeled-ASCs at a minimum of 1×10^5 cells/ml/microtube using 1.5 and 3T MRI, but the detection sensitivity was lower with T2-weighted sequences (T2).

Conclusions: Iron sucrose incubation is a safe alternative method for ASCs labeling and tracking using MRI following treatment. Clinicians and researchers should be able to visualize the location of ASCs engraftment without secondary surgical investigation involving tissue sampling.

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Mesenchymal Stem Cells Mediated Drug Delivery in Tumor-Targeted Therapy

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Abstract

Mesenchymal stem cells (MSCs) possess unique properties that make them potential carriers for cancer therapy. MSCs have been documented to have low immunogenicity, positive safety in clinical trials, and the ability to selectively homing to inflammation and tumor sites. Thisreview aims to introduce tumor tropism mechanism and effects of MSCs on tumor cells, and give an overview of MSCs in delivering gene therapeutic agents, oncolytic viruses and chemotherapeutics, as well as the application of MSCs-derived exosomes in tumor-targeted therapy.

Front Bioeng Biotechnol

. 2020 Jul 23;8:748.
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Recent Advances on Drug-Loaded Mesenchymal Stem Cells With Anti-neoplastic Agents for Targeted Treatment of Cancer

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- PMID: 32793565
- PMCID: PMC7390947
- DOI: 10.3389/fbioe.2020.00748

Free PMC article

Abstract

Mesenchymal stem cells (MSCs), as an undifferentiated group of adult multipotent cells, have remarkable antitumor features that bring them up as a novel choice to treat cancers. MSCs are capable of altering the behavior of cells in the tumor microenvironment, inducing an anti-inflammatory effect in tumor cells, inhibiting tumor angiogenesis, and preventing metastasis. Besides, MSCs can induce apoptosis and inhibit the proliferation of tumor cells. The ability of MSCs to be loaded with chemotherapeutic drugs and release them in the site of primary and metastatic neoplasms makes them a preferable choice as targeted drug delivery procedure. Targeted drug delivery minimizes unexpected side effects of chemotherapeutic drugs and improves clinical outcomes. This review focuses on recent advances on innate antineoplastic features of MSCs and the effect of chemotherapeutic drugs on viability, proliferation, and the regenerative capacity of various kinds of MSCs. It also discusses the efficacy and mechanisms of drug loading and releasing procedures along with *in vivo* and *in vitro* preclinical outcomes of antineoplastic effects of primed MSCs for clinical prospection.

Cytotherapy
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. 2020 Aug 5;S1465-3249(20)30790-8.
doi: 10.1016/j.jcyt.2020.07.004. Online ahead of print.

Indirect co-culture of lung carcinoma cells with hyperthermia-treated mesenchymal stem cells influences tumor spheroid growth in a collagen-based 3-dimensional microfluidic model

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- PMID: 32771259

- DOI: 10.1016/j.jcyt.2020.07.004

Abstract

Background: Mesenchymal stem cells (MSCs) have paradoxically been reported to exert either pro- or anti-tumor effects in vitro. Hyperthermia, in combination with chemotherapy, has tumor-inhibiting effects; however, its role, together with MSCs, so far is not well understood. Furthermore, a lot of research is conducted using conventional 2-dimensional in vitro models that do not mimic the actual tumor microenvironment.

Aim: In light of this fact, an indirect method of co-culturing human amniotic membrane-derived MSCs (AMMSCs) with collagen-encapsulated human lung carcinoma cells (A549) was performed using a 3-dimensional (3D) tumor-on-chip device.

Methods: The conditioned medium of AMMSCs (AMMSC-CM) or heat-treated AMMSCs (heat-AMMSC-CM) was utilized to create indirect co-culture conditions. Tumor spheroid growth characterization, immunocytochemistry and cytotoxicity assays, and anti-cancer peptide (P1) screening were performed to determine the effects of the conditioned medium.

Results: The A549 cells cultured inside the 3D microfluidic chip developed into multicellular tumor spheroids over five days of culture. The AMMSC-CM, contrary to previous reports claiming its tumor-inhibiting potential, led to significant proliferation of tumor spheroids. Heat-AMMSC-CM led to reductions in both spheroid diameter and cell proliferation. The medium containing the P1 peptide was found to be the least cytotoxic to tumor spheroids in co-culture compared with the monoculture and heat-co-culture groups.

Conclusions: Hyperthermia, in combination with the anticancer peptide, exhibited highest cytotoxic effects. This study highlights the growing importance of 3D microfluidic tumor models for testing stem-cell-based and other anti-cancer therapies.