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Exosomes derived from bone marrow mesenchymal stem cells promote osteosarcoma development by activating oncogenic autophagy.

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Abstract

Osteosarcoma (OS) is a malignant bone tumor that frequently occurs in adolescents. It has a high rate of pulmonary metastasis and mortality. Previous studies have demonstrated that human bone marrow mesenchymal stem cells (hBMSCs) can promote the malignant progression in various tumors, including OS. Also, it is recognized that exosomes derived from hBMSCs (hBMSC-Exos) mediate cell-to-cell communication and exhibit similar effects on the development of various tumors. However, the role of hBMSC-Exos in the development of OS is still unclear and the underlying mechanism needs to be elucidated. Our results show that hBMSC-derived exosomes promote OS cell proliferation, migration, and invasion. Meanwhile, silencing autophagy-related gene 5 (ATG5) in OS cells abolishes the pro-tumor effects of hBMSC-Exos *in vitro* and *in vivo.* Our present study demonstrates that hBMSC-Exos promotes tumorigenesis and metastasis by promoting oncogenic autophagy in OS.

Cytotherapy. 2020 Feb 14. pii: S1465-3249(20)30005-0. doi: 10.1016/j.jcyt.2020.01.004. [Epub ahead of print]

Improving mesenchymal stem/stromal cell potency and survival: Proceedings from the International Society of Cell Therapy (ISCT) MSC preconference held in May 2018, Palais des Congrès de Montréal, Organized by the ISCT MSC Scientific Committee.

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Abstract

As part of the International Society of Cell Therapy (ISCT) 2018 Annual Meeting, the Mesenchymal Stem/Stromal Cell (MSC) committee organized a pre-conference, which covered methods of improving MSC engraftment and potency in vivo and clinical efficacy using MSC potency assays. The speakers examined methods to improve clinical efficacy using MSC potency assays and methods to improve MSC engraftment/homing/potency in vivo. Discussion of patient "responders" versus "non-responders" in clinical trials and working toward ways to identify them were also included.

Mol Biol Rep. 2020 Feb 17. doi: 10.1007/s11033-020-05311-y. [Epub ahead of print]

Evaluation of the stability of standard reference genes of adipose-derived mesenchymal stem cells during in vitro proliferation and differentiation.

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Abstract

Mesenchymal stem cells (MSCs) from a variety of sources are being used in pre-clinical and clinical studies. The choice of optimal source for treatment of diseases requires quantitative evaluation of self-renewal, proliferation and differentiation potencies of MSCs. For this purpose, quantitative real-time polymerase chain reaction (qRT-PCR) technique is used to determine the expression of genes. qRT-PCR requires the normalization of the gene expression levels by the use of reference genes in order to obtain accurate and reliable results. There is a limited number of studies focused on the selection of reference genes that are appropriate and reliable for MSCs. Thus, no single reference gene has yet been found for use in the in vitro proliferation and differentiation of MSCs. The aim of this study is to investigate the stability of the expression of widely used reference genes during the in vitro proliferation and differentiation of human adipose-derived mesenchymal stem cells (hASCs). For this purpose, 13 reference genes commonly used in MSC studies were selected. As a result, the expression stabilities of EF1α, RPLP0 and RPL13A genes were found to be high and were predicted to be suitable for use as reference genes for normalization in hASC studies. The GAPDH was identified as the gene with the lowest expression stability and evaluated to be an unsuitable reference gene for hASC differentiation studies. This piece of information could be crucial for the selection of appropriate reference genes and accurate measurement of gene expression in hASC studies.

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Functional dosing of mesenchymal stromal cell-derived extracellular vesicles for the prevention of acute graft-versus-host-disease.

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Abstract

Graft-vs-host-disease (GvHD) is currently the main complication of allogeneic hematopoietic stem cell transplantation. Mortality and morbidity rates are particularly high, especially in steroid-refractory acute GvHD (aGvHD). Immune regulatory human bone marrow mesenchymal stromal cells (hMB-MSCs) represent a therapeutic approach to address this issue. Unfortunately, their effect is hardly predictable in vivo due to several variables, that is, MSC tissue origin, concentration, dose number, administration route and timing, and inflammatory status of the recipient. Interestingly, human bone marrow MSC-derived extracellular vesicles (hBM-MSC-EVs) display many of the hBM-MSC immunoregulatory properties due to their content in paracrine factors that greatly varies according to the collection method. In this study, we focused on the immunological characterization of hBM-MSC-EVs on their

capability of inducing regulatory T-cells (T-regs) both in vitro and in a xenograft mouse model of aGvHD. We correlated these data with the aGvHD incidence and degree following hBM-MSC-EV intravenous administration. Thus, we first quantified the EV immunomodulation in vitro in terms of EV immunomodulatory functional unit (EV-IFU), that is, the lowest concentration of EVs leading in vitro to at least threefold increase of the T-regs compared with controls. Second, we established the EV therapeutic dose in vivo (EV-TD) corresponding to 10-fold the in vitro EV-IFU. According to this approach, we observed a significant improvement of both mouse survival and control of aGvHD onset and progression. This study confirms that EVs may represent an alternative to whole MSCs for aGvHD prevention, once the effective dose is reproducibly identified according to EV-IFU and EV-TD definition.

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Extracellular vesicles from human liver stem cells inhibit renal cancer stem cell-derived tumor growth in vitro and in vivo.

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Abstract

Cancer stem cells (CSCs) are considered as responsible of initiation, maintenance and recurrence of solid tumors, thus representing the key for tumor eradication. The anti-tumor activity of extracellular vesicles (EVs) derived from different stem cell sources has been investigated with conflicting results. In this study, we evaluated, both in vitro and in vivo, the effect of EVs derived from human bone marrow mesenchymal stromal cells (MSCs) and from a population of human liver stem cells (HLSCs) of mesenchymal origin on renal CSCs. In vitro, both EV sources displayed pro-apoptotic, anti-proliferative and anti-invasive effects on renal CSCs, but not on differentiated tumor cells. Pre-treatment of renal CSCs with EVs, before subcutaneous injection in SCID mice, delayed tumor onset. We subsequently investigated the in vivo effect of MSC- and HLSC-EVs systemic administration on progression of CSC-generated renal tumors. Tumor bio-distribution analysis identified intravenous treatment as best route of administration. HLSC-EVs, but not MSC-EVs, significantly impaired subcutaneous tumor growth by reducing tumor vascularization and inducing tumor cell apoptosis. Moreover, intravenous treatment with HLSC-EVs improved the metastasis-free survival. In EV treated tumor explants, we observed both the transfer and the induction of miR-145 and of miR-200 family members. In transfected CSCs, the same miRNAs affected cell growth, invasion and survival. In conclusion, our results showed a specific anti-tumor effect of HLSC-EVs on CSC-derived renal tumors in vivo, possibly ascribed to the transfer and induction of specific anti-tumor miRNAs. This study provides further evidence for a possible clinical application of stem cell-EVs in tumor treatment.

Tissue Eng Part A. 2020 Feb 19. doi: 10.1089/ten.TEA.2019.0206. [Epub ahead of print]

Human ASC Spheroids Possess High Adipogenic Capacity and Acquire an Adipose Tissue-like ECM Pattern.

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Abstract

Adipose-derived mesenchymal stromal/stem cells (ASCs) represent a commonly used cell source for adipose tissue engineering. In this context, ASCs have routinely been cultured in conventional 2D culture and applied as single cell suspension for seeding onto scaffold materials or direct injection. However, this approach is associated with the loss of their intrinsic 3D microenvironment and leads to impaired regenerative capacity of the cells. Thus, the application of ASCs as self-assembled 3D spheroids with cells residing in their own matrix is an attractive alternative. However, characterization of their structural features and differentiation capacity is necessary in order to effectively apply them as building blocks in adipose tissue engineering. In this study, we focus on extracellular matrix (ECM) development in ASC spheroids, as well as adipogenic differentiation in comparison to conventional 2D culture using different induction protocols. Reproducible assembly of ASCs into spheroids was achieved within 24 h using the liquid overlay technique. Undifferentiated spheroids displayed a stromal ECM pattern, with fibronectin, collagen V and VI as the main components. In the course of adipogenesis, a dynamic shift in the ECM composition towards an adipogenic phenotype was observed, associated with enhanced expression of laminin, collagen I, IV, V and VI, similar to native fat. Further, adipogenic differentiation was enhanced in spheroids as compared to 2D cultured cells, with the spheroids needing a distinctly shorter adipogenic stimulus to sustain adipogenesis, which was demonstrated based on analysis of triglyceride content and adipogenic marker gene expression. In summary, culturing ASC as spheroids can enhance their adipogenic capacity and generate adipose-like microtissues, which may be a promising cell delivery strategy for adipose tissue engineering approaches.