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Bone marrow mesenchymal stem cell-derived exosomes promote plasminogen activator inhibitor 1 expression in vascular cells in the local microenvironment during rabbit osteonecrosis of the femoral head

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Free PMC article

Abstract

Background: Nontraumatic osteonecrosis of the femoral head (NONFH) is a highly disabling orthopedic disease in young individuals. Plasminogen activator inhibitor 1 (PAI-1) has been reported to be positively associated with NONFH. We aimed to investigate the dysregulating PAI-1 in bone marrow mesenchymal stem cells (BMMSCs) and vascular cells in rabbit steroid-induced NONFH.

Methods: To verify the hypothesis that BMMSCs could promote thrombus formation in a paracrine manner, we collected exosomes from glucocorticoid-treated BMMSCs (GB-Exo)

to determine their regulatory effects on vascular cells. microRNA sequencing was conducted to find potential regulators in GB-Exo. Utilizing gain-of-function and knockdown approaches, we testified the regulatory effect of microRNA in exosomes.

Results: The expression of PAI-1 was significantly increased in the local microenvironment of the femoral head in the ONFH model. GB-Exo promoted PAI-1 expression in vascular smooth muscle cells and vascular endothelial cells. We also revealed that miR-451-5p in GB-Exo plays a crucial role for the elevated PAI-1. Moreover, we identified miR-133b-3p and tested its role as a potential inhibitor of PAI-1.

Conclusions: This study provided considerable evidence for BMMSC exosomal miR-mediated upregulation of the fibrinolytic regulator PAI-1 in vascular cells. The disruption of coagulation and low fibrinolysis in the femoral head will eventually lead to a disturbance in the microcirculation of NONFH. We believe that our findings could be of great significance for guiding clinical trials in the future.

Heliyon
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Establishment of human immortalized mesenchymal stem cells lines for the monitoring and analysis of osteogenic differentiation in living cells

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Abstract

Mesenchymal stem cells (MSCs) are expected to be useful in bone regeneration treatment for various diseases and conditions, including cleft lip and palate, fracture, and bone absorption. However, to date, MSCs have failed to produce satisfactory results in clinical settings. This is primarily due to the low rate of induced osteogenic differentiation. To realize MSC potential, it is necessary to establish methods for the isolation of MSC-derived living osteoblasts. However, no osteoblast markers have been reported to date. In an attempt to develop a method for the assessment of osteoblast differentiation, we established reporter human immortalized MSC (hiMSC) lines for *in vitro* monitoring of bone gamma-carboxyglutamate protein (BGLAP, osteocalcin) expression. To this end, we successfully knocked-in an enhanced green fluorescent protein (EGFP) gene cassette immediately downstream of the first ATG of BGLAP via CRISPR-Cas9, and established hiMSC lines expressing EGFP to monitor osteogenic differentiation. On differentiation day 7, EGFP-positive cells were collected by flow cytometric cell sorting, and the expression of EGFP and endogenous BGLAP was analyzed. During osteogenic differentiation, EGFP upregulation was found to correlate with expression of endogenous BGLAP. Moreover, mineralization was confirmed using Alizarin red-S staining after two weeks of osteogenic differentiation of the modified hiMSC lines. The modified hiMSC lines, as well as the derived differentiated osteoblasts obtained herein, are valuable tools for the monitoring osteoblast gene and protein expression, and can be used to develop novel methods for isolating living osteoblasts.

Adv Exp Med Biol

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Interests of Exosomes in Bone and Periodontal Regeneration: A Systematic Review

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Abstract

Periodontitis is an infectious inflammatory disease characterized by clinical attachment loss and tooth supporting tissue destruction. As exosomes demonstrated pro-regenerative ability, their use in periodontal treatment has been suggested. The aim of this systematic review is to gather and summarize the most recent data regarding exosomes to determine their potential impact in bone and periodontal regeneration. Electronic databases (Pubmed, Web of Science) were searched up to February 2020. Studies assessing the impact of exosomes administration in experimental bone and periodontal defects have been identified according to PRISMA guidelines. Among the 183 identified articles, 16 met the inclusion criteria and were included in this systematic review. Experimental bone defects were mainly surgically induced with a dental bur or distraction tools. All studies considered bone healing after exosomes administration as the primary outcome. Results showed that mesenchymal stem cells derived exosomes administration promoted bone healing and neovascularization. Nevertheless, a dose-effect relationship was observed. Exosomes administration appears to promote significantly the bone healing and periodontal regeneration. However, only a limited number of studies have been carried out so far and the optimized protocols in this context need to be evaluated.

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Altered Tumor Plasticity after Different Cancer Cell Fusions with MSC

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Abstract

While cell fusion demonstrates an important pathway during tissue development and regeneration of distinct organs, this process can also contribute to pathophysiological phenotypes during tumor progression. Hybrid cell formation after heterofusion between cancer cells and various other cell types within the tumor microenvironment is observed in vitro and in vivo. In particular, mesenchymal stroma/stem-like cells (MSC) perform diverse levels of communication with cancer cells by exhibiting anti- and pro-tumorigenic effects. During these cellular interactions, MSC can eventually fuse with cancer cells. Thereby, the newly generated disparate hybrid populations display aneuploidy associated with chromosomal instability. Based upon a subsequent post-hybrid selection process (PHSP), fused cancer cells can undergo apoptosis/necroptosis, senescence, dormancy, or a proliferative state by acquisition of new properties. Consequently, PHSP-surviving hybrid cancer cells demonstrate altered functionalities within the tumor tissue. This is accompanied by changes in therapeutic responsiveness and a different metastatic behavior. Accordingly, enhanced tumor plasticity interferes with successful therapeutic interventions and aggravates patient prognoses. The present review article focusses on fusion of MSC with different human cancer cells, in particular breast cancer populations and resulting characteristics of various cancer hybrid cells. Moreover, some mechanisms of cancer cell fusion are discussed together with multiple PHSP pathways.

Immun Inflamm Dis

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Secreted TRAIL gene-modified adipose-derived stem cells exhibited potent tumor-suppressive effect in hepatocellular carcinoma cells

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Abstract

Objective: Considering the potential of adipose-derived stem cells (ADSCs) migrating towards cancer cells, this study was performed to explore the function of tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) modified ADSCs on the development and progression of hepatocellular carcinoma (HCC).

Methods: ADSCs were extracted from human adipose tissues and identified through immunofluorescence and flow cytometry. Oil red staining and alizarin red staining were performed to clarify the differentiation potential of ADSCs. AAV-CMV-sTRAIL was transfected into ADSCs before Western blot and Transwell measurements. sTRAIL-ADSCs were cocultured with HCC cells to explore its effect on the proliferation and apoptosis of HCC cells. The possible effect of sTRAIL-ADSCs or ADSCs on tumor growth and metastasis was determined in vivo using xenograft nude mouse models.

Results: ADSCs were successfully extracted from adipose tissues, which were confirmed by cell morphology and positive expressions of CD44 and CD105. ADSCs were found with differentiation potential. After transfection, TRAIL was stably expressed in sTRAIL-ADSCs. Both ADSCs and sTRAIL-ADSCs can migrate towards HCC cells. In addition, sTRAIL-ADSCs can promote the cell apoptosis and inhibit cell proliferation in vitro, on parallel it can also suppress epithelial-mesenchymal transition, tumor growth, and metastasis in vivo.

Conclusion: TRAIL modified ADSCs can migrate towards HCC cells to inhibit tumor growth and the metastasis of implanted HCC tumors, which hints TRAIL modified ADSCs may be a new therapeutic approach for HCC treatment.