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Insights into Inflammatory Priming of Adipose-Derived Mesenchymal Stem Cells: Validation of Extracellular Vesicles-Embedded miRNA Reference Genes as A Crucial Step for Donor Selection.

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Author information

Abstract

Mesenchymal stem cells (MSCs) are promising tools for cell-based therapies due to their homing to injury sites, where they secrete bioactive factors such as cytokines, lipids, and nucleic acids, either free or conveyed within extracellular vesicles (EVs). Depending on the local environment, MSCs' therapeutic value may be modulated, determining their fate and cell behavior. Inflammatory signals may induce critical changes on both the phenotype and secretory portfolio. Intriguingly, in animal models resembling joint diseases as osteoarthritis (OA), inflammatory priming enhanced the healing capacity of MSC-derived EVs. In this work, we selected miRNA reference genes (RGs) from the literature (let-7a-5p, miR-16-5p, miR-23a-3p, miR-26a-5p, miR-101-3p, miR-103a-3p, miR-221-3p, miR-423-5p, miR-425-5p, U6 snRNA), using EVs isolated from adipose-derived MSCs (ASCs) primed with IFNγ (iASCs). geNorm, NormFinder, BestKeeper, and ΔCt methods identified miR-26a-5p/16-5p as the most stable, while miR-103a-rp/425-5p performed poorly. Our results were validated on miRNAs involved in OA cartilage trophism. Only a proper normalization strategy reliably identified the differences between donors, a critical factor to empower the therapeutic value of future off-the-shelf MSC-EV isolates. In conclusion, the proposed pipeline increases the accuracy of MSC-EVs embedded miRNAs assessment, and help predicting donor variability for precision medicine approaches.

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The effects of graphene and mesenchymal stem cells in cutaneous wound healing and their putative action mechanism.

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Abstract

This study provides a review of the therapeutic potential of graphene dressing scaffolds and mesenchymal stem cells (MSCs) and their synergistic effects with respect to cutaneous wound healing. This study also considers their putative action mechanism based on the antibacterial, immunomodulating, angiogenic, matrix remodeling effects of materials belonging to the graphene family and MSCs during the wound healing process. In addition, this study discusses the cytocompatibility of

graphene, its uses as a platform for skin substitutes, the properties it possesses with respect to providing protection against microbial invasion as well as strategies aimed at minimizing the chance of the occurrence of sepsis. MSCs are capable of secreting several factors that exert a therapeutic impact on reparative processes and tissue regeneration. In light of experiments conducted to date, graphene combined with MSCs appears to have the potential to enhance both the wound healing process and infection control at the injury site.

Stem Cells Int. 2019 Mar 18;2019:4957806. doi: 10.1155/2019/4957806. eCollection 2019.

Equine Adipose-Derived Mesenchymal Stromal Cells Release Extracellular Vesicles Enclosing Different Subsets of Small RNAs.

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Abstract

BACKGROUND:

Equine adipose-derived mesenchymal stromal cells (e-AdMSC) exhibit attractive proregenerative properties strongly related to the delivery of extracellular vesicles (EVs) that enclose different kinds of molecules including RNAs. In this study, we investigated small RNA content of EVs produced by e-AdMSC with the aim of speculating on their possible biological role.

METHODS:

EVs were obtained by ultracentrifugation of the conditioned medium of e-AdMSC of 4 subjects. Transmission electron microscopy and scanning electron microscopy were performed to assess their size and nanostructure. RNA was isolated, enriched for small RNAs (<200 nt), and sequenced by Illumina technology. After bioinformatic analysis with state-of-the-art pipelines for short sequences, mapped reads were used to describe EV RNA cargo, reporting classes, and abundances. Enrichment analyses were performed to infer involved pathways and functional categories.

RESULTS:

Electron microscopy showed the presence of vesicles ranging in size from 30 to 300 nm and expressing typical markers. RNA analysis revealed that ribosomal RNA was the most abundant fraction, followed by small nucleolar RNAs (snoRNAs, 13.67%). Miscellaneous RNA (misc_RNA) reached 4.57% of the total where Y RNA, RNaseP, and vault RNA represented the main categories. miRNAs were sequenced at a lower level (3.51%) as well as protein-coding genes (1.33%). Pathway analyses on the protein-coding fraction revealed a significant enrichment for the "ribosome" pathway followed by "oxidative phosphorylation." Gene Ontology analysis showed enrichment for terms like "extracellular exosome," "organelle envelope," "RNA binding," and "small molecule metabolic process." The miRNA target pathway analysis revealed the presence of "signaling pathways regulating pluripotency of stem cells" coherent with the source of the samples.

CONCLUSION:

We herein demonstrated that e-AdMSC release EVs enclosing different subsets of small RNAs that potentially regulate a number of biological processes. These findings shed light on the role of EVs in the context of MSC biology.

Cancers (Basel). 2019 Apr 21;11(4). pii: E568. doi: 10.3390/cancers11040568.

MSC.sTRAIL Has Better Efficacy than MSC.FL-TRAIL and in Combination with AKTi Blocks Pro-Metastatic Cytokine Production in Prostate Cancer Cells.

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Abstract

Cell therapy is a promising new treatment option for cancer. In particular, mesenchymal stem cells (MSCs) have shown potential in delivering therapeutic genes in various tumour models and are now on the verge of being tested in the clinic. A number of therapeutic genes have been examined in this context, including the death ligand TRAIL. For cell therapy, it can be used in its natural form as a full-length and membrane-bound protein (FL-TRAIL) or as an engineered version commonly referred to as soluble TRAIL (sTRAIL). As to which is more therapeutically efficacious, contradicting results have been reported. We discovered that MSCs producing sTRAIL have significantly higher apoptosis-inducing activity than cells expressing FL-TRAIL and found that FL-TRAIL, in contrast to sTRAIL, is not secreted. We also demonstrated that TRAIL does induce the expression of pro-metastatic cytokines in prostate cancer cells, but that this effect could be overcome through combination with an AKT inhibitor. Thus, a combination consisting of small-molecule drugs specifically targeting tumour cells in combination with MSC.sTRAIL, not only provides a way of sensitising cancer cells to TRAIL, but also reduces the issue of side-effect-causing cytokine production. This therapeutic strategy therefore represents a novel targeted treatment option for advanced prostate cancer and other difficult to treat tumours.

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Metastatic Niches and the Modulatory Contribution of Mesenchymal Stem Cells and Its Exosomes.

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Abstract

Mesenchymal stem cells (MSCs) represent an interesting population due to their capacity to release a variety of cytokines, chemokines, and growth factors, and due to their motile nature and homing ability. MSCs can be isolated from different sources, like adipose tissue or bone marrow, and have the capacity to differentiate, both in vivo and in vitro, into adipocytes, chondrocytes, and osteoblasts, making them even more interesting in the regenerative medicine field. Tumor associated stroma has been recognized as a key element in tumor progression, necessary for the biological success of the

tumor, and MSCs represent a functionally fundamental part of this associated stroma. Exosomes represent one of the dominant signaling pathways within the tumor microenvironment. Their biology raises high interest, with implications in different biological processes involved in cancer progression, such as the formation of the pre-metastatic niche. This is critical during the metastatic cascade, given that it is the formation of a permissive context that would allow metastatic tumor cells survival within the new environment. In this context, we explored the role of exosomes, particularly MSCs-derived exosomes as direct or indirect modulators. All this points out a possible new tool useful for designing better treatment and detection strategies for metastatic progression, including the management of chemoresistance.

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A pilot study of human mesenchymal stem cells from visceral and sub-cutaneous fat tissue and their differentiation to osteogenic phenotype.

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Abstract

OBJECTIVE:

To evaluate the different behavior of two different human adult adipocytes derived stem cells (hASCs) during proliferation and osteogenic differentiation.

PATIENTS AND METHODS:

Human adult adipocytes stem cells (hAT-SCs) from visceral (hAV-SCs) and subcutaneous (hAS-SCs) sites were obtained after surgery procedures of seven patients. All samples were fully investigated and the different proliferation rates were evaluated. All MSCs clusters were cultured with an osteogenic and adipogenic differentiation medium. Homogeneous pools of Mesenchymal Stem Cells (MSCs) were confirmed by Flow-Cytometry Analysis (FACS) and Spectrophotometric Assay. The differentiated cells were eventually assessed for the expression of Alkaline Phosphatase (ALP), Alizarin Red (AR) and Oil Red-O (OR-O) detection, and analyzed by the Spectrophotometric Assay. After osteogenic differentiation, the cell clusters were incubated and analyzed with Real Time-Polymerase Chain Reaction (qRT-PCR) and fluorescence microscopy.

RESULTS:

The FACS analysis performed on hAT-SCs confirmed the homogenous presence of MSCs in all samples. The ALP, AR stain confirmed the osteogenic differentiation capacity of MSCs towards osteoblast-like-cells. The colorimetric cell metabolic activity (MTS) assay showed an increase in the proliferation rate with different values in both sets hAS-SCs vs. hAV-SCs.

CONCLUSIONS:

These in vitro findings of both hAS-SCs and hAV-SCs suggested an important role of these stem cells for future clinical use in bone regeneration. Indeed, the final outcomes suggested a better performance of cells coming from subcutaneous adipose tissue vs. those from visceral fat tissue.

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Menstrual blood-derived stem cells as delivery vehicles for oncolytic adenovirus virotherapy for colorectal cancer.

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Abstract

Oncolytic adenoviruses (Ads) have potential applications in cancer therapy due to their ability to replicate and induce tumor cell death. However, their clinical application has been limited by the lack of efficient cell based delivery systems that can provide protection from immune attack and prevent virus clearance by neutralizing antibodies. We previously demonstrated that menstrual blood-derived mesenchymal stem cells (MenSCs) can specifically target tumor cells and serve as a novel drug delivery platform. We engineered CRAd5/F11 chimeric oncolytic Ads that can infect MenSCs and preserve their tumor targeting ability in vitro. MenSCs loaded with these Ads were transplanted in a mouse tumor model. We found that a large number of the CRAd5/F11 viruses were accumulated in tumor site and mediated marked inhibitory effects against CRC. Thus, we conclude that MenSC-cloaked oncolytic Ads hold great potential as a novel virus-delivery platform for the therapy of various cancers including CRC.

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Mesenchymal stem cells pretreated with platelet-rich plasma modulate doxorubicin-induced cardiotoxicity.

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Abstract

The cardiotoxic adverse effect of doxorubicin (DOX) is the major factor limiting its use. Recently, mesenchymal stem cells (MSCs) have been implicated in the preclinical studies of treatment of DOX-induced cardiotoxicity. The question is MSCs pretreated with platelet-rich plasma (PRP) have a better influence on DOX-induced cardiotoxicity compared to the influence of MSCs alone. Twenty-four Wistar rats were categorized into control, DOX-treated, MSC-treated, and PRP/MSC-treated groups. DOX was injected for two consecutive weeks. Light microscopic, biochemical markers (interleukin 10 (IL-10), tumor necrosis factor alpha (TNF-α), and creatine kinase-MB (CK-MB)), immunohistochemical (Bax, Bcl2, vascular endothelial growth factor (VEGF), and cardiac troponin-I (CT-I)), and oxidative/antioxidative markers (malondialdehyde (MDA)/superoxide dismutase (SOD)) were measured. Degenerative cardiac changes were detected in the DOX-treated group with complete loss of the architecture and coagulative necrosis. These changes were accompanied with the elevation of

the serum level of CK-MB and loss of CT-I immunoreactivity. The major factors in the DOX-induced cardiotoxicity were the oxidative stress (elevated MDA/decreased SOD), inflammation (elevated TNF-α/decreased IL-10), and cardiac apoptosis (lower Bcl2, higher Bax, and lower Bcl2/Bax ratio). MSCs and PRP/MSCs attenuate DOX-induced cardiotoxicity. Better attenuation was observed in the PRP/MSC-treated group. PRP/MSC combination reduced greatly the MDA and TNF-α and increased IL-10, Bcl2/Bax ratio, and VEGF. PRP had no significant influence over the Bcl2, Bax, and SOD. In conclusion, DOX in its toxic dose induced myocardial injury. This destructive effect is related to oxidative stress, inflammation, and cardiac apoptosis. PRP/MSC possesses a better attenuation over the DOX-induced toxicity compared to MSC alone.