ML 11-19 (30/03/2019)

Crit Rev Oncol Hematol. 2019 Mar 9. pii: S1040-8428(19)30045-9. doi: 10.1016/j.critrevonc.2019.03.002. [Epub ahead of print]

Exosome-transferred lncRNAs at the core of cancer bone lesions.

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Abstract

Exosome-mediated transfer of regulatory RNAs is a key feature that enables cancer cells to shape a tumor-promoting environment. Cancers growing in the bone can use this communication modality to disrupt the homeostatic balance between bone forming and bone resorbing cells, which results in the release of bone-embedded factors supporting cancer growth and progression. Long noncoding RNAs (lncRNAs) are potent regulators of cell fate determination with exceptional cell- and tissue-specificity that are secreted by cancer cells via exosomes. In multiple myeloma (MM), the exosomal transfer of the lncRNA RUNX2-AS1 specifically inhibits the osteogenic differentiation capacity of mesenchymal stem cells (MSC) by repressing the master regulator of bone formation RUNX2. Detailed studies into the role of exosomal lncRNA transfer in the bone microenvironment in vivo might constitute the basis for the development of novel therapeutic strategies for tumor-associated bone lesions.

Stem Cell Res Ther. 2019 Mar 19;10(1):101. doi: 10.1186/s13287-019-1200-6.

Impact of HOXB7 overexpression on human adipose-derived mesenchymal progenitors.

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Abstract

BACKGROUND:

The ex vivo expansion potential of mesenchymal stromal/stem cells (MSC) together with their differentiation and secretion properties makes these cells an attractive tool for transplantation and tissue engineering. Although the use of MSC is currently being tested in a growing number of clinical trials, it is still desirable to identify molecular markers that may help improve their performance both in vitro and after transplantation.

METHODS:

Recently, HOXB7 was identified as a master player driving the proliferation and differentiation of bone marrow mesenchymal progenitors. In this study, we investigated the effect of HOXB7 overexpression on the ex vivo features of adipose mesenchymal progenitors (AD-MSC).

RESULTS:

HOXB7 increased AD-MSC proliferation potential, reduced senescence, and improved chondrogenesis together with a significant increase of basic fibroblast growth factor (bFGF) secretion.

CONCLUSION:

While further investigations and in vivo models shall be applied for better understanding, these data suggest that modulation of HOXB7 may be a strategy for innovative tissue regeneration applications.

Int J Mol Sci. 2019 Mar 16;20(6). pii: E1340. doi: 10.3390/ijms20061340.

Hypoxia-Regulated miRNAs in Human Mesenchymal Stem Cells: Exploring the Regulatory Effects in Ischemic Disorders.

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Abstract

Human mesenchymal/stromal stem cells (hMSC) are the most promising cell source for adult cell therapies in regenerative medicine. Many clinical trials have reported the use of autologous transplantation of hMSCs in several disorders, but with limited results. To exert their potential, hMSCs could exhibit efficient homing and migration toward lesion sites among other effects, but the underlying process is not clear enough. To further increase the knowledge, we studied the co-regulation between hypoxia-regulated genes and miRNAs. To this end, we investigated the miRNA expression profile of healthy hMSCs in low oxygen/nutrient conditions to mimic ischemia and compared with cells of patients suffering from critical limb ischemia (CLI). miRNAs are small, highly conserved, non-coding RNAs, skilled in the control of the target's expression level in a fine-tuned way. After analyzing the miRNOme in CLI-derived hMSC cells and healthy controls, and intersecting the results with the mRNA expression dataset under hypoxic conditions, we identified two miRNAs potentially relevant to the disease: miR-29b as a pathological marker of the disease and miR-638 as a therapeutic target. This study yielded a deeper understanding of stem cell biology and ischemic disorders, opening new potential treatments in the future.

ACS Appl Mater Interfaces. 2019 Mar 27. doi: 10.1021/acsami.8b22685. [Epub ahead of print]

Safe and Effective Delivery of Antitumor Drug Using Mesenchymal Stem Cells Impregnated with Submicron Carriers.

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Abstract

An important area in modern malignant tumor therapy is the optimization of antitumor drugs pharmacokinetics. The use of some antitumor drugs is limited in clinical practice due to their high

toxicity. Therefore, the strategy for optimizing the drug pharmacokinetics focuses on the generation of high local concentrations of these drugs in the tumor area with minimal systemic and tissue-specific toxicity. This can be achieved by encapsulation of highly toxic antitumor drug (vincristine (VCR) that is 20-50 times more toxic than widely used the antitumor drug doxorubicin) into nano- and microcarriers with their further association into therapeutically relevant cells that possess the ability to migrate to sites of tumor. Here, we fundamentally examine the effect of drug carrier size on the behavior of human mesenchymal stem cells (hMSCs), including internalization efficiency, cytotoxicity, cell movement, to optimize the conditions for the development of carrier-hMSCs drug delivery platform. Using the malignant tumors derived from patients, we evaluated the capability of hMSCs associated with VCR-loaded carriers to target tumors using a three-dimensional spheroid model in collagen gel. Compared to free VCR, the developed hMSC-based drug delivery platform showed enhanced antitumor activity regarding those tumors that express CXCL12 (stromal cell-derived factor-1 (SDF-1)) gene, inducing directed migration of hMSCs via CXCL12 (SDF-1)/CXCR4 pathway. These results show that the combination of encapsulated antitumor drugs and hMSCs, which possess the properties of active migration into tumors, is therapeutically beneficial and demonstrated high efficiency and low systematic toxicity, revealing novel strategies for chemotherapy in the future.

Stem Cells Cloning. 2019 Mar 1;12:11-16. doi: 10.2147/SCCAA.S181883. eCollection 2019.

Treatment of osteonecrosis of the femoral head by core decompression and implantation of fully functional ex vivo-expanded bone marrow-derived mesenchymal stem cells: a proof-of-concept study.

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Abstract

BACKGROUND:

Based on several attributes involved in bone formation, bone marrow-resident mesenchymal stem cells (MSCs) have been employed in the treatment of patients suffering from femoral head osteonecrosis. Due to the low content of MSCs in the bone marrow, ex vivo expansion procedures are utilized to increase the cell number. Customarily, before administration of the resulting expanded cell product MSCs to the patient, its cellular identity is usually evaluated according to a set of "minimal phenotypic" markers, which are not modified by ex vivo processing. However, MSC functional ("reparative") markers, which are severely impaired along the ex vivo expansion routine, are usually not assessed.

PATIENTS AND METHODS:

In this proof-of-concept study, a cohort of five avascular osteonecrosis patients received an instillation of ex vivo-expanded autologous MSCs, manufactured under controlled conditions, with an aim to protect their functional ("reparative") capacity.

RESULTS AND CONCLUSION:

Outcomes of this study confirmed the safety and effectiveness of the MSC-based therapy used. After a follow-up period (19-54 months), in all patients, the hip function was significantly improved and pain intensity markedly reduced. As a corollary, no patient required hip arthroplasty.

Acta Biomater. 2019 Mar 15. pii: S1742-7061(19)30197-7. doi: 10.1016/j.actbio.2019.03.031. [Epub ahead of print]

Synchrotron radiation techniques boost the research in bone tissue engineering.

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Abstract

X-ray Synchrotron radiation-based techniques, in particular Micro-tomography and Micro-diffraction, were exploited to investigate the structure of bone deposited in vivo within a porous ceramic scaffold. Bone formation was studied by implanting Mesenchymal Stem Cell (MSC) seeded ceramic scaffolds in a mouse model. Osteoblasts derived from the seeded MSC and from differentiation of cells migrated within the scaffold together with the blood vessels, deposited within the scaffold pores an organic collagenous matrix on which a precursor mineral amorphous liquid-phase, containing Ca++ and PO_4^{--} crystallized filling the gaps between the collagen molecules. Histology offered a valid instrument to investigate the engineered tissue structure, but, unfortunately, limited itself to a macroscopic analysis. The evolution of the X-ray Synchrotron radiation-based techniques and the combination of micro X-ray diffraction with X-ray phase-contrast imaging enabled to study the dynamic of the structural and morphological changes occurring during the new bone deposition, biomineralization and vascularization. In fact, the unique features of Synchrotron radiation, is providing the high spatial resolution probe which is necessary for the study of complex materials presenting heterogeneity from micron-scale to meso- and nano-scale. Indeed, this is the occurrence in the heterogeneous and hierarchical bone tissue where an organic matter, such as the collagenous matrix, interacts with mineral nano-crystals to generate a hybrid multiscale biomaterial with unique physical properties. In this framework, the use of advanced synchrotron radiation techniques allowed to understand and to clarify fundamental aspects of the bone formation process within the bioceramic, i.e. biomineralization and vascularization, including to obtain deeper knowledge on bone deposition, mineralization and reabsorption in different health, aging and pathological conditions. In this review we present an overview of the X-ray Synchrotron radiation techniques and we provide a general outlook of their applications on bone Tissue Engineering, with a focus on our group work. STATEMENT OF SIGNIFICANCE: Synchrotron Radiation techniques for Tissue Engineering In this review we report recent applications of X-ray Synchrotron radiation-based techniques, in particular Microtomography and Microdiffraction, to investigations on the structure of ceramic scaffolds and bone tissue regeneration. Tissue engineering has made significant advances in bone regeneration by proposing the use of mesenchymal stem cells in combination with various types of scaffolds. The efficacy of the biomaterials

used to date is not considered optimal in terms of resorbability and bone formation, resulting in a poor vascularization at the implant site. The review largely based on our publications in the last ten years could help the study of the regenerative model proposed. We also believe that the new imaging technologies we describe could be a starting point for the development of additional new techniques with the final aim of transferring them to the clinical practice.

Cell Death Dis. 2019 Mar 19;10(4):264. doi: 10.1038/s41419-019-1508-2.

Bone marrow-derived mesenchymal stem cells promote colorectal cancer progression via CCR5.

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Abstract

Mesenchymal stem cells (MSCs) are recruited from BM to the stroma of developing tumors, where they serve as critical components of the tumor microenvironment by secreting growth factors, cytokines, and chemokines. The role of MSCs in colorectal cancer (CRC) progression was controversial. In this study, we found that C-C chemokine receptor type 5 (CCR5) ligands (i.e., C-C motif chemokine ligand 3 (CCL3), CCL4, and CCL5) were highly produced from MSCs using a chemokine array screening with conditioned media from the cultured human MSCs. A relatively strong CCR5 expression could be detected within the cytoplasm of several CRC cell lines. Regarding the effect of MSC, we found that the xenografts in which CCR5-overexpressing HCT116 cells were inoculated into immunocompromised mice were highly promoted in vivo by a mixture with MSCs. Notably, the CCR5 inhibitor, maraviroc, significantly abolished the MSC-induced tumor growth in vivo. In human clinical specimens (n = 89), 20 cases (29%) were high for CCR5, whereas 69 cases (71%) were low. Statistical analyses indicated that CCR5 expression in primary CRC was associated with CRC patients' prognosis. Especially, stage III/IV patients with CCR5-high CRCs exhibited a significantly poorer prognosis than those with CCR5-low CRCs. Furthermore, we investigated the effects of preoperative serum CCR5 ligands on patients' prognosis (n = 114), and found that CRC patients with high serum levels of CCL3 and CCL4 exhibited a poorer prognosis compared to those with low levels of CCL3 and CCL4, while there was no association between CCL5 and prognosis. These results suggest that the inhibition of MSC-CRC interaction by a CCR5 inhibitor could provide the possibility of a novel therapeutic strategy for CRC, and that serum levels of CCL3 and CCL4 could be predictive biomarkers for the prognosis of CRC patients.