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Macrophages activate mesenchymal stem cells to acquire cancer-associated fibroblast-like features resulting in gastric epithelial cell lesions and malignant transformation *in vitro*.

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Author information

Abstract

The majority of premalignant gastric lesions develop in the mucosa that has been modified by chronic inflammation. As components of the gastritis microenvironment, mesenchymal stem cells (MSCs) and macrophages are critically involved in the initiation and development of the chronic gastritis-associated gastric epithelial lesions/malignancy process. However, in this process, the underlying mechanism of macrophages interacting with MSCs, particularly the effect of macrophages on MSCs phenotype and function remains to be elucidated. The present study revealed that human umbilical cord-derived MSCs were induced to differentiate into cancer-associated fibroblasts (CAFs) phenotype by co-culture with macrophages (THP-1 cells) *in vitro*, and which resulted in gastric epithelial lesions/potential malignancy via epithelial-mesenchymal transition-like changes. The results of the present study indicated that macrophages could induce MSCs to acquire CAF-like features and a pro-inflammatory phenotype to remodel the inflammatory microenvironment, which could potentiate oncogenic transformation of gastric epithelium cells. The present study provides potential targets and options for inflammation-associated gastric cancer prevention and intervention.

Stem Cells Dev. 2019 Jan 18. doi: 10.1089/scd.2018.0152. [Epub ahead of print]

Identification of a Novel Transcription Factor Required For Osteogenic Differentiation Of Mesenchymal Stem Cells.

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Abstract

Osteogenic differentiation is a complex and still poorly understood biological process regulated by intrinsic cellular signals and extrinsic micro-environmental cues. Following appropriate stimuli, mesenchymal stem cells (MSCs) differentiate into osteoblasts through a tightly regulated multi-step process driven by several transcription factors and characterized by the expression of a number of bone-specific proteins. Here, we describe a novel transcription factor that we named Osteoblast Inducer (Obl)-1, involved in MSC differentiation towards the osteogenic lineage. Obl-1 encodes for a nuclear protein subjected to proteasomal degradation and expressed during osteoblast differentiation both in a murine multipotent mesenchymal cell line (W20-17) and in primary murine MSCs. RNAi-mediated knockdown of Obl-1 expression significantly impairs osteoblast differentiation and matrix mineralization

with reduced expression of the osteogenic markers Runx2 and osteopontin. Conversely, ObI-1 over-expression enhances osteogenic differentiation and bone-specific markers expression. ObI-1 stimulates bone-morphogenetic protein (BMP)-4 expression and the consequent activation of the Smad pathway; treatment with a BMP receptor-type I antagonist completely abolishes ObI-1-mediated stimulation of osteogenic differentiation. Collectively, our findings suggest that ObI-1 modulates osteogenic differentiation, at least in part, through the BMP signaling pathway, increasing Runx2 activation and leading to osteoblast commitment and maturation.

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Scalable MSC-Derived Bone Tissue Modules: In Vitro Assessment of Differentiation, Matrix Deposition, and Compressive Load Bearing.

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Abstract

Enhancements to the mechanical properties of modular designs for bone tissue engineering could increase their clinical applications. In this study, bone marrow mesenchymal stem cells (MSCs) and hydroxyapatite (HAP) microgranules were encapsulated in polyelectrolyte complex membranes composed of chondroitin 4-sulfate (C4S), carboxymethyl cellulose (CMC) and chitosan. Microcapsules were formed with and without HAP microgranules, and cultured in either osteoinduction medium (Osteo) or expansion medium (Exp) to produce four microcapsule conditions: Osteo, Osteo+HAP, Exp, and Exp+HAP. Microcapsules facilitated alkaline phosphatase secretion and deposition of bone specific proteins (osteocalcin and osteopontin) by encapsulated MSCs over 28 days of osteogenic culture. SEM and micro-CT analysis showed cell-deposited mineral covering the surfaces of the HAP microgranules and interior of the microcapsule membrane. The mineralized microcapsules could be combined and fused into cylindrical constructs (4 x 5 mm, W x H), and uniaxial compression tests confirmed that microcapsule mineralization greatly enhanced the yield stresses of Osteo and Osteo+HAP fused constructs (10.4 ± 4.4 MPa and 6.4 ± 2.8 MPa), compared to only HAP microgranules (Exp+HAP , 0.5 ± 0.3 MPa). The C4S/CMC/Chitosan microcapsules provide a platform allowing pre-mineralization of microcapsules in vitro for later assembly of larger load-bearing constructs, or for use as an injectable bone regeneration strategy. STATEMENT OF SIGNIFICANCE: Clinical translation of bone tissue engineering is limited by the difficulty of generating space filling implants that both resist compressive loading, and simultaneously deliver cells throughout the bone defect. Here, we present the design of a microcapsule system containing both stem cells capable of rebuilding bone tissue, and a mechanically tough bone-like mineral, that imparts compression resistance to the microcapsules. The microcapsules support stem cell differentiation to an osteogenic phenotype, that can mineralize the microcapsule membrane and interior. The mineralized microcapsules can be assembled into larger bone constructs, and have mechanical properties on par with trabecular bone.

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Conditioned media serived from mesenchymal stem cell cultures: The next generation for regenerative medicine.

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Abstract

Recent studies suggest that the main driving force behind the therapeutic activity observed in mesenchymal stem cells (MSCs) are the paracrine factors secreted by these cells. These biomolecules also trigger anti-apoptotic events to prevent further degeneration of the diseased organ through paracrine signalling mechanisms. In comparison to the normal physiological conditions, an increased paracrine gradient is observed within the peripheral system of diseased organs which enhances the migration of tissue specific MSCs towards the site of infection or injury to promote healing. Thus, upon administration of conditioned media derived from mesenchymal stem cell cultures (MSC-CM) could contribute in maintaining the increased paracrine factor gradient between the diseased organ and the stem cell niche in order to speed up the process of recovery. Based on the principle of the paracrine signalling mechanism, MSC-CM, also referred as the secretome of the MSCs, is a rich source of the paracrine factors and are being studied extensively for a wide range of regenerative therapies such as myocardial infarction, stroke, bone regeneration, hair growth and wound healing. This article highlights the current technological applications and advances of MSC-CM with the aim to appraise its future potential as a regenerative therapeutic agent.

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Spontaneous formation of tumorigenic hybrids between human omental adipose-derived stromal cells and endometrial cancer cells increased motility and heterogeneity of cancer cells.

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Abstract

Recent reports indicate that mesenchymal stem cells (MSCs) can fuse with cancer cells to promote cancer progression. Omental adipose-derived stromal cells (O-ASCs) are similar to MSCs, which could be recruited to the stroma in endometrial cancer. The aim of our study was to investigate whether O-ASCs can fuse with endometrial cancer cells to influence cancer cells biological characteristics We isolated O-ASCs from patients with endometrial cancer. O-ASCs and endometrial cancer cells were labeled with different fluorescent tags and directly co-cultured in an Opera high-throughput spinning-disk confocal microscopy system to observe the processes involved in the fusion, division and migration of hybrid cells. Immunofluorescence and high-throughput imaging analyses were performed to evaluate proteins related to epithelial-mesenchymal transition (EMT).We found O-ASCs could spontaneously fuse with endometrial cancer cells, including cytomembrane and nuclear fusion. After fusion,

endometrial cancer cells assume an elongated and fibroblast-like appearance that exhibit mesenchymal phenotypes. The hybrid cells proliferated through bipolar and multipolar divisions and exhibited more rapid migratory speeds than were observed in the parental cells (P<0.01), potentially because of their EMT-associated changes, including the down-regulation of E-cadherin and up-regulation of Vimentin. Our results collectively suggest that tumorigenic hybrids spontaneously formed between human O-ASCs and endometrial cancer cells, and that the resulting cells enhanced cancer mobility and heterogeneity by accelerated migration and undergoing multipolar divisions. These data provide a new avenue for investigating the roles of O-ASCs in endometrial cancer.

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An updated review of adipose derived-mesenchymal stem cells and their applications in musculoskeletal disorders.

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Abstract

Adipose-derived mesenchymal stem cells (ASCs) represent a new therapeutic strategy in biomedicine with many potential applications, especially in musculoskeletal disorders. Preclinical and clinical studies based on the administration of ASCs support their efficacy in bone regeneration, joint repair, tendon injury and skeletal muscle alterations. Many of these novel treatments may improve patients' quality of life and prognosis. However, several concerns about the use of stem cells remain unsolved, particularly regarding their safety and side effects. The present work aims to review the nature, clinical trials and patents involving the use of ASCs in musculoskeletal disorders. Area covered: In this article, we describe ASCs' isolation, culture and differentiation in vivo and in vitro, advances on ASCs' applications in bone, cartilage, muscle and tendon repair, and patents involving the use of ASCs. Expert opinion: The use of ASCs in musculoskeletal disorders presents significant therapeutic advantages, including limited autoimmune response, potential cell expansion ex vivo, high plasticity to differentiate into several mesodermal cell lineages, and additional effects of therapeutic interest such as secretion of neurotrophic factors and anti-inflammatory properties. For these reasons, ASCs are promising therapeutic agents for clinical applications in musculoskeletal disorders.