ALS Pathogenesis and Therapeutic Approaches: The Role of Mesenchymal Stem Cells and Extracellular Vesicles.

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Author information

Abstract

Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disease characterized by progressive muscle paralysis determined by the degeneration of motoneurons in the motor cortex brainstem and spinal cord. The ALS pathogenetic mechanisms are still unclear, despite the wealth of studies demonstrating the involvement of several altered signaling pathways, such as mitochondrial dysfunction, glutamate excitotoxicity, oxidative stress and neuroinflammation. To date, the proposed therapeutic strategies are targeted to one or a few of these alterations, resulting in only a minimal effect on disease course and survival of ALS patients. The involvement of different mechanisms in ALS pathogenesis underlines the need for a therapeutic approach targeted to multiple aspects. Mesenchymal stem cells (MSC) can support motoneurons and surrounding cells, reduce inflammation, stimulate tissue regeneration and release growth factors. On this basis, MSC have been proposed as promising candidates to treat ALS. However, due to the drawbacks of cell therapy, the possible therapeutic use of extracellular vesicles (EVs) released by stem cells is raising increasing interest. The present review summarizes the main pathological mechanisms involved in ALS and the related therapeutic approaches proposed to date, focusing on MSC therapy and their preclinical and clinical applications. Moreover, the nature and characteristics of EVs and their role in recapitulating the effect of stem cells are discussed, elucidating how and why these vesicles could provide novel opportunities for ALS treatment.

Mesenchymal Stem Cell-Derived Extracellular Vesicles: Roles in Tumor Growth, Progression, and Drug Resistance.

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Author information

Abstract

Mesenchymal stem cells (MSCs) are ubiquitously present in many tissues. Due to their unique advantages, MSCs have been widely employed in clinical studies. Emerging evidences indicate that MSCs can also migrate to the tumor surrounding stroma and exert complex effects on tumor growth and progression. However, the effect of MSCs on tumor growth is still a matter of debate. Several studies have shown that MSCs could favor tumor growth. On the contrary, other groups have demonstrated that MSCs suppressed tumor progression. Extracellular vesicles have emerged as a new mechanism of cell-to-cell communication in the development of tumor diseases. MSCs-derived
extracellular vesicles (MSC-EVs) could mimic the effects of the mesenchymal stem cells from which they originate. Different studies have reported that MSC-EVs may exert various effects on the growth, metastasis, and drug response of different tumor cells by transferring proteins, messenger RNA, and microRNA to recipient cells. In the present review, we summarize the components of MSC-EVs and discuss the roles of MSC-EVs in different malignant diseases, including the related mechanisms that may account for their therapeutic potential. MSC-EVs open up a promising opportunity in the treatment of cancer with increased efficacy.


The geometrical shape of mesenchymal stromal cells measured by quantitative shape descriptors is determined by the stiffness of the biomaterial and by cyclic tensile forces.

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Abstract

Controlling mesenchymal stromal cell (MSC) shape is a novel method for investigating and directing MSC behaviour in vitro. It was hypothesized that specific MSC shapes can be generated by using stiffness-defined biomaterial surfaces and by applying cyclic tensile forces. Biomaterials used were thin and thick silicone sheets, fibronectin coating, and compacted collagen type I sheets. The MSC morphology was quantified by shape descriptors describing dimensions and membrane protrusions. Nanoscale stiffness was measured by atomic force microscopy and the expression of smooth muscle cell (SMC) marker genes (ACTA2, TAGLN, CNN1) by quantitative reverse-transcription polymerase chain reaction. Cyclic stretch was applied with 2.5% or 5% amplitudes. Attachment to biomaterials with a higher stiffness yielded more elongated MSCs with fewer membrane protrusions compared with biomaterials with a lower stiffness. For cyclic stretch, compacted collagen sheets were selected, which were associated with the most elongated MSC shape across all investigated biomaterials. As expected, cyclic stretch elongated MSCs during stretch. One hour after cessation of stretch, however, MSC shape was rounder again, suggesting loss of stretch-induced shape. Different shape descriptor values obtained by different stretch regimes correlated significantly with the expression levels of SMC marker genes. Values of approximately 0.4 for roundness and 3.4 for aspect ratio were critical for the highest expression levels of ACTA2 and CNN1. Thus, specific shape descriptor values, which can be generated using biomaterial-associated stiffness and tensile forces, can serve as a template for the induction of specific gene expression levels in MSC.


Intranuclear Actin Structure Modulates Mesenchymal Stem Cell Differentiation.
Actin structure contributes to physiologic events within the nucleus to control mesenchymal stromal cell (MSC) differentiation. Continuous cytochalasin D (Cyto D) disruption of the MSC actin cytoskeleton leads to osteogenic or adipogenic differentiation, both requiring mass transfer of actin into the nucleus. Cyto D remains extranuclear, thus intranuclear actin polymerization is potentiated by actin transfer: we asked whether actin structure affects differentiation. We show that secondary actin filament branching via the Arp2/3 complex is required for osteogenesis and that preventing actin branching stimulates adipogenesis, as shown by expression profiling of osteogenic and adipogenic biomarkers and unbiased RNA-seq analysis. Mechanistically, Cyto D activates osteoblast master regulators (e.g., Runx2, Sp7, Dlx5) and novel coregulated genes (e.g., Atoh8, Nr4a3, Slfn5). Formin-induced primary actin filament formation is critical for Arp2/3 complex recruitment: osteogenesis is prevented by silencing of the formin mDia1, but not its paralog mDia2. Furthermore, while inhibition of actin, branching is a potent adipogenic stimulus, silencing of either mDia1 or mDia2 blocks adipogenic gene expression. We propose that mDia1, which localizes in the cytoplasm of multipotential MSCs and traffics into the nucleus after cytoskeletal disruption, joins intranuclear mDia2 to facilitate primary filament formation before mediating subsequent branching via Arp2/3 complex recruitment. The resulting intranuclear branched actin network specifies osteogenic differentiation, while actin polymerization in the absence of Arp2/3 complex-mediated secondary branching causes adipogenic differentiation.


Peptide-Coated Semiconductor Polymer Dots for Stem Cells Labeling and Tracking.

Meng Z, Guo L, Li Q.  

Abstract  
Stem cell therapy is rapidly moving toward translation to clinical application. To elucidate the therapeutic effect, a robust method that allows tracking of the stem cells over an extended period of time is highly required. Here, we demonstrate semiconducting polymer dots (Pdots) for bright labeling and tracking of human mesenchymal stem cells (MSCs) in vitro and in vivo. The Pdots coated with a cell penetrating peptide (R8) showed remarkable endocytic uptake efficiency that was 15 times higher than that of carboxyl Pdots and more than 200 times than that of bare Pdots. The Pdot-labeled MSCs can be traced for 14 generations in vitro and tracked over 2 weeks in vivo after subcutaneous transplantation. The labeled MSCs administered via tail vein were preferentially accumulated in the lung, distinctive from the distribution of free Pdots that were primarily distributed in the liver. Based on the properties of the bright labeling, excellent tracking capability and great biocompatibility, the Pdots will be valuable in the applications of stem cell biology and regenerative medicine.

Adipose-Derived Mesenchymal Stem Cells for Treatment of Airway Injuries in A Patient after Long-Term Exposure to Sulfur Mustard.

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Author information
Abstract

OBJECTIVE:
Sulfur mustard (SM) is a potent mutagenic agent that targets several organs, particularly lung tissue. Changes in morphological structure of the airway system are associated with chronic obstructive pulmonary deficiency following exposure to SM. Although numerous studies have demonstrated pathological effects of SM on respiratory organs, unfortunately there is no effective treatment to inhibit further respiratory injuries or induce repair in these patients. Due to the extensive progress and achievements in stem cell therapy, we have aimed to evaluate safety and potential efficacy of systemic mesenchymal stem cell (MSC) administration on a SM-exposed patient with chronic lung injuries.

MATERIALS AND METHODS:
In this clinical trial study, our patient received 100×10⁶ cells every 20 days for 4 injections over a 2-month period. After each injection we evaluated the safety, pulmonary function tests (PFT), chronic obstructive pulmonary disease (COPD) Assessment Test (CAT), St. George’s Respiratory Questionnaire (SGRQ), Borg Scale Dyspnea Assessment (BSDA), and 6 Minute Walk Test (6MWT). One-way ANOVA test was used in this study which was not significant (P>0.05).

RESULTS:
There were no infusion toxicities or serious adverse events caused by MSC administration. Although there was no significant difference in PFTs, we found a significant improvement for 6MWT, as well as BSDA, SGRQ, and CAT scores after each injection.

CONCLUSION:
Systemic MSC administration appears to be safe in SM-exposed patients with moderate to severe injuries and provides a basis for subsequent cell therapy investigations in other patients with this disorder (Registration Number: IRCT2015110524890N1).


Enhanced osteogenic differentiation of rat bone marrow mesenchymal stem cells on titanium substrates by inhibiting Notch3.

Wang H¹, Jiang Z², Zhang J², Xie Z¹, Wang Y³, Yang G⁴.

Author information
Abstract
**OBJECTIVE:**
The role of the Notch pathway has already been identified as a crucial regulator of bone development. However, the Notch signaling pathway has gone largely unexplored during osseointegration. This study aims to investigate the role of Notch signaling on osteogenic differentiation of rat derived bone marrow mesenchymal stem cells (BMSCs) on sandblasted, large-grit, acid-etched (SLA) treated Ti disks.

**METHODS:**
The involved target genes in Notch pathways were identified by in vitro microarray and bioinformatics analyses with or without osteogenic induction. Adhesion, proliferation, and osteogenic related assay were subsequently conducted with target gene shRNA treatment.

**RESULTS:**
We found that 11 genes in the Notch signaling pathway were differentially expressed after osteogenic induction on SLA-treated Ti disks, which included up-regulated genes (Notch2, Dll1, Dll3, Ncstn, Ncor2, and Hes5) and down-regulated genes (Notch3, Lfng, Mfng, Jag2 and Maml2). With Notch3 shRNA treatment, the adhesion and proliferation of BMSCs on SLA-treated Ti disks were inhibited. Moreover, the expression levels of alkaline phosphatase (ALP), osteocalcin (OCN), calcium deposition, BMP2 and Runx2 increased significantly compared with that observed in control groups, suggesting that the function of Notch3 was inhibitory in the osteogenic differentiation of BMSCs on SLA-treated titanium.

**CONCLUSIONS:**
Inhibition Notch3 can enhance osteogenic differentiation of BMSCs on SLA-treated Ti disks, which potentially provides a gene target for improving osseointegration.


**The effect of extracellular acidosis on the behaviour of mesenchymal stem cells in vitro.**


**Author information**

**Abstract**

The stem cell fraction of a cell population is finely tuned by stimuli from the external microenvironment. Among these stimuli, a decrease of extracellular pH (pHe) may occur in a variety of physiological and pathological conditions, including hypoxia and inflammation. In this study, by using bone marrow stem cells and dental pulp stem cells, we provided evidence that extracellular acidosis endows the maintenance of stemness in mesenchymal cells. Indeed, continuous exposure for 21 d to low pHe (6.5-6.8) conditions impaired the osteogenic differentiation of both cell types. Moreover, the exposure to low pHe, for 1 and up to 7 d, induced the expression of stemness-related genes and proteins, drove cells to reside in the quiescent G0 alert state and enhanced their ability to form floating spheres. The pre-conditioning with extracellular acidosis for 7 d did not affect the differentiation potential of dental pulp stem cells since, when the cells were cultured again at physiological pHe, their multilineage potential was almost unmodified. Our data provided evidence of the role of extracellular acidosis as a modulator
of the stemness of mesenchymal cells. This condition is commonly found both in systemic and local bone conditions, hence underlining the relevance of this phenomenon for a better comprehension of bone healing and regeneration.