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Tissue regeneration: The crosstalk between mesenchymal stem cells and immune response.

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Author information

Abstract

Mesenchymal stem cells (MSCs) exist in almost all tissues with the capability to differentiate into several different cell types and hold great promise in tissue repairs in a cell replacement manner. The study of the bidirectional regulation between MSCs and immune response has ushered an age of rethinking of tissue regeneration in the process of stem cell-based tissue repairs. By sensing damaged signals, both endogenous and exogenous MSCs migrate to the damaged site where they involve in the reconstitution of the immune microenvironment and empower tissue stem/progenitor cells and other resident cells, whereby facilitate tissue repairs. This MSC-based therapeutic manner is conferred as cell empowerment. In this process, MSCs have been found to exert extensive immunosuppression on both innate and adaptive immune response, while such regulation needs to be licensed by inflammation. More importantly, the immunoregulation of MSCs is highly plastic, especially in the context of pathological microenvironment. Understanding the immunoregulatory properties of MSCs is necessary for appropriate application of MSCs. Here we review the current studies on the crosstalk of MSCs and immune response in disease pathogenesis and therapy.

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Aspirin inhibits the proliferation of synovium-derived mesenchymal stem cells by arresting the cell cycle in the G0/G1 phase.

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Abstract

Mesenchymal stem cells (MSCs) provide promising applications for clinical treatments. However, patients often take medications that affect the viability of transplanted MSCs. The aim of this study was to assess the effects and underlying mechanism of action of aspirin on the proliferation of MSCs. We showed that aspirin inhibited the growth of MSCs in a concentration- and time-dependent manner. Analysis of cell-cycle distributions showed significantly increased cell populations in the G0/G1 phase and decreased cell populations in the S phase and G2/M phase with increasing concentrations of aspirin. We further analyzed the expression of cyclins and found that the level of cyclin D1 was significantly reduced after aspirin treatment, while there was no obvious effect on the levels of cyclin A2 and cyclin E1. Because we showed that the expression of miRNA145 was significantly increased after aspirin treatment, we further transfected MSCs with an miRNA145 mimic or miRNA145 inhibitor.

Transfection with the miRNA145 mimic resulted in decreased expression of cyclin D1, while transfection with miRNA145 inhibitor resulted in increased expression of cyclin D1. Transfection with miRNA145 inhibitor abolished the downregulation of cyclin D induced by aspirin. The results suggested that aspirin inhibited the proliferation of MSCs and caused cell-cycle arrest in the G0/G1 phase through downregulation of cyclin D1, which could be related to the increased expression of miRNA145.

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3D microniches reveal the importance of cell size and shape.

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Abstract

Geometrical cues have been shown to alter gene expression and differentiation on 2D substrates. However, little is known about how geometrical cues affect cell function in 3D. One major reason for this lack of understanding is rooted in the difficulties of controlling cell geometry in a complex 3D setting and for long periods of culture. Here, we present a robust method to control cell volume and shape of individual human mesenchymal stem cells (hMSCs) inside 3D microniches with a range of different geometries (e.g., cylinder, triangular prism, cubic, and cuboid). We find that the actin filaments, focal adhesions, nuclear shape, YAP/TAZ localization, cell contractility, nuclear accumulation of histone deacetylase 3, and lineage selection are all sensitive to cell volume. Our 3D microniches enable fundamental studies on the impact of biophysical cues on cell fate, and have potential applications in investigating how multicellular architectures organize within geometrically well-defined 3D spaces.

Stem Cell Res Ther. 2017 Dec 6;8(1):277. doi: 10.1186/s13287-017-0730-z.

Preconditioning of murine mesenchymal stem cells synergistically enhanced immunomodulation and osteogenesis.

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Abstract

BACKGROUND:

Mesenchymal stem cells (MSCs) are capable of immunomodulation and tissue regeneration, highlighting their potential translational application for treating inflammatory bone disorders. MSC-mediated immunomodulation is regulated by proinflammatory cytokines and pathogen-associated molecular patterns such as lipopolysaccharide (LPS). Previous studies showed that MSCs exposed to interferon gamma (IFN-γ) and the proinflammatory cytokine tumor necrosis factor alpha (TNF-α) synergistically suppressed T-cell activation.

METHODS:

In the current study, we developed a novel preconditioning strategy for MSCs using LPS plus TNF-α to optimize the immunomodulating ability of MSCs on macrophage polarization.

RESULTS:

Preconditioned MSCs enhanced anti-inflammatory M2 macrophage marker expression (Arginase 1 and CD206) and decreased inflammatory M1 macrophage marker (TNF-α/IL-1Ra) expression using an in-vitro coculture model. Immunomodulation of MSCs on macrophages was significantly increased compared to the combination of IFN-γ plus TNF-α or single treatment controls. Increased osteogenic differentiation including alkaline phosphate activity and matrix mineralization was only observed in the LPS plus TNF-α preconditioned MSCs. Mechanistic studies showed that increased prostaglandin E2 (PGE2) production was associated with enhanced Arginase 1 expression. Selective cyclooxygenase-2 inhibition by Celecoxib decreased PGE2 production and Arginase 1 expression in cocultured macrophages.

CONCLUSIONS:

The novel preconditioned MSCs have increased immunomodulation and bone regeneration potential and could be applied to the treatment of inflammatory bone disorders including periprosthetic osteolysis, fracture healing/nonunions, and osteonecrosis.

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Clinical Implications of Bone Marrow Adiposity.

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Abstract

Marrow adipocytes, collectively termed marrow adipose tissue (MAT), reside in the bone marrow in close contact to bone cells and hematopoietic cells. Marrow adipocytes arise from the mesenchymal stem cell and share their origin with the osteoblastst. Shifts in the lineage allocation of the mesenchymal stromal cell could potentially explain the association between increased MAT and increased fracture risk in diseases such as postmenopausal osteoporosis, anorexia nervosa and diabetes. Functionally, marrow adipocytes secrete adipokines, such as adiponectin, and cytokines, such as RANK-ligand and stem cell factor. These mediators can influence both bone remodeling and hematopoiesis by promoting bone resorption and hematopoietic recovery following chemotherapy. In addition, marrow adipocytes can secrete free fatty acids, acting as a energy supply for bone and hematopoietic cells. However, this induced lipolysis is also used by neoplastic cells to promote survival and proliferation. Therefore, MAT could represent a new therapeutic target for multiple diseases from osteoporosis to leukemia, although the exaxt characteristics and role of the marrow adipocyte in health and diseases remains to be determined.

Stem Cells Transl Med. 2017 Dec 6. doi: 10.1002/sctm.17-0209. [Epub ahead of print]

Concise Review: Quantitative Detection and Modeling the In Vivo Kinetics of Therapeutic Mesenchymal Stem/Stromal Cells.

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Abstract

Mesenchymal stem/stromal cells (MSCs) present a promising tool in cell-based therapy for treatment of various diseases. Currently, optimization of treatment protocols in clinical studies is complicated by the variations in cell dosing, diverse methods used to deliver MSCs, and the variety of methods used for tracking MSCs in vivo. Most studies use a dose escalation approach, and attempt to correlate efficacy with total cell dose. Optimization could be accelerated through specific understanding of MSC distribution in vivo, long-term viability, as well as their biological fate. While it is not possible to quantitatively detect MSCs in most targeted organs over long time periods after systemic administration in clinical trials, it is increasingly possible to apply pharmacokinetic modeling to predict their distribution and persistence. This Review outlines current understanding of the in vivo kinetics of exogenously administered MSCs, provides a critical analysis of the methods used for quantitative MSC detection in these studies, and discusses the application of pharmacokinetic modeling to these data. Finally, we provide insights on and perspectives for future development of effective therapeutic strategies using pharmacokinetic modeling to maximize MSC therapy and minimize potential side effects.

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Culture Medium Supplements Derived from Human Platelet and Plasma: Cell Commitment and Proliferation Support.

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Abstract

Present cell culture medium supplements, in most cases based on animal sera, are not fully satisfactory especially for the *in vitro* expansion of cells intended for human cell therapy. This paper refers to (i) an heparin-free human platelet lysate (PL) devoid of serum or plasma components (v-PL) and (ii) an heparin-free human serum derived from plasma devoid of PL components (Pl-s) and to their use as single components or in combination in primary or cell line cultures. Human mesenchymal stem cells (MSC) primary cultures were obtained from adipose tissue, bone marrow, and umbilical cord. Human chondrocytes were obtained from articular cartilage biopsies. In general, MSC expanded in the presence of Pl-s alone showed a low or no proliferation in comparison to cells grown with the combination of Pl-s and v-PL. Confluent, growth-arrested cells, either human MSC or human articular chondrocytes, treated with v-PL resumed proliferation, whereas control cultures, not supplemented with v-PL, remained quiescent and did not proliferate. Interestingly, signal transduction pathways distinctive of proliferation were activated also in cells treated with v-PL in the absence of serum, when cell

proliferation did not occur, indicating that v-PL could induce the cell re-entry in the cell cycle (cell commitment), but the presence of serum proteins was an absolute requirement for cell proliferation to happen. Indeed, Pl-s alone supported cell growth in constitutively activated cell lines (U-937, HeLa, HaCaT, and V-79) regardless of the co-presence of v-PL. Plasma- and plasma-derived serum were equally able to sustain cell proliferation although, for cells cultured in adhesion, the Pl-s was more efficient than the plasma from which it was derived. In conclusion, the cells expanded in the presence of the new additives maintained their differentiation potential and did not show alterations in their karyotype.