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Secretion, migration and adhesion as key processes in the therapeutic activity of mesenchymal stem cells.

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Abstract

The MSCs are immature cells that can be found in numerous different tissue types. In recent years, they have gained considerable attention, particularly with regard to their regenerative properties. Due to their paracrine activity, ability to migrate, adhesion and homing, MSCs currently appear to be the most relevant for therapeutic use. Numerous bioactive molecules secreted by MSCs exert paracrine effects and modulate many physiological processes, such as angiogenesis, immunomodulation and neuroprotection. Cell-cell communication may be also mediated by extracellular vesicles released from the cells. Due to these properties, MSCs have been widely studied for evaluation of their therapeutic benefits expected in the clinical applications. For effective tissue regeneration, transplanted MSCs have to exit the circulation and locate at the site of damage, which is possible because of their ability to migrate, adhere and engraft at the target site. Accumulating evidence suggests that MSCs recruitment from remote sites is similar to leukocytes' migration. All of these biological features make MSCs highly investigated stem cells and the most commonly used cells in regenerative medicine. Since environmental factors affect the MSCs behavior, we discuss importance of oxygen concentration as a one of the key factors affecting MSCs properties.

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Injectable, scalable 3D tissue-engineered model of marrow hematopoiesis.

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Abstract

Modeling the interaction between the supportive stroma and the hematopoietic stem and progenitor cells (HSPC) is of high interest in the regeneration of the bone marrow niche in blood disorders. In this work, we present an injectable co-culture system to study this interaction in a coherent in vitro culture and in vivo transplantation model. We assemble a 3D hematopoietic niche in vitro by co-culture of supportive OP9 mesenchymal cells and HSPCs in porous, chemically defined collagen-coated carboxymethylcellulose microscaffolds (CCMs). Flow cytometry and hematopoietic colony forming assays demonstrate the stromal supportive capacity for in vitro hematopoiesis in the absence of exogenous cytokines. After in vitro culture, we recover a paste-like living injectable niche biomaterial from CCM co-cultures by controlled, partial dehydration. Cell viability and the association between

stroma and HSPCs are maintained in this process. After subcutaneous injection of this living artificial niche in vivo, we find maintenance of stromal and hematopoietic populations over 12 weeks in immunodeficient mice. Indeed, vascularization is enhanced in the presence of HSPCs. Our approach provides a minimalistic, scalable, biomimetic in vitro model of hematopoiesis in a microcarrier format that preserves the HSPC progenitor function, while being injectable in vivo without disrupting the cell-cell interactions established in vitro.

Micromachines (Basel). 2019 Dec 25;11(1). pii: E31. doi: 10.3390/mi11010031.

3D Printed Wavy Scaffolds Enhance Mesenchymal Stem Cell Osteogenesis.

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Abstract

There is a growing interest in developing 3D porous scaffolds with tunable architectures for bone tissue engineering. Surface topography has been shown to control stem cell behavior including differentiation. In this study, we printed 3D porous scaffolds with wavy or linear patterns to investigate the effect of wavy scaffold architecture on human mesenchymal stem cell (hMSC) osteogenesis. Five distinct wavy scaffolds were designed using sinusoidal waveforms with varying wavelengths and amplitudes, and orthogonal scaffolds were designed using linear patterns. We found that hMSCs attached to wavy patterns, spread by taking the shape of the curvatures presented by the wavy patterns, exhibited an elongated shape and mature focal adhesion points, and differentiated into the osteogenic lineage. When compared to orthogonal scaffolds, hMSCs on wavy scaffolds showed significantly enhanced osteogenesis, indicated by higher calcium deposition, alkaline phosphatase activity, and osteocalcin staining. This study aids in the development of 3D scaffolds with novel architectures to direct stem osteogenesis for bone tissue engineering.

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Small molecules for mesenchymal stem cell fate determination.

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Abstract

Mesenchymal stem cells (MSCs) are adult stem cells harboring self-renewal and multilineage differentiation potential that are capable of differentiating into osteoblasts, adipocytes, or chondrocytes *in vitro*, and regulating the bone marrow microenvironment and adipose tissue remodeling *in vivo*. The process of fate determination is initiated by signaling molecules that drive MSCs into a specific lineage. Impairment of MSC fate determination leads to different bone and adipose tissue-related diseases, including aging, osteoporosis, and insulin resistance. Much progress has been made in recent years in discovering small molecules and their underlying mechanisms control the cell fate of MSCs both *in vitro* and *in vivo*. In this review, we summarize recent findings in applying

small molecules to the trilineage commitment of MSCs, for instance, genistein, medicarpin, and icariin for the osteogenic cell fate commitment; isorhamnetin, risedronate, and arctigenin for pro-adipogenesis; and atractylenolides and dihydroartemisinin for chondrogenic fate determination. We highlight the underlying mechanisms, including direct regulation, epigenetic modification, and post-translational modification of signaling molecules in the AMPK, MAPK, Notch, PI3K/AKT, Hedgehog signaling pathways *etc*. and discuss the small molecules that are currently being studied in clinical trials. The target-based manipulation of lineage-specific commitment by small molecules offers substantial insights into bone marrow microenvironment regulation, adipose tissue homeostasis, and therapeutic strategies for MSC-related diseases.

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Influence of olive oil and its components on mesenchymal stem cell biology.

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Abstract

Extra virgin olive oil is characterized by its high content of unsaturated fatty acid residues in triglycerides, mainly oleic acid, and the presence of bioactive and antioxidant compounds. Its consumption is associated with lower risk of suffering chronic diseases and unwanted processes linked to aging, due to the antioxidant capacity and capability of its components to modulate cellular signaling pathways. Consumption of olive oil can alter the physiology of mesenchymal stem cells (MSCs). This may explain part of the healthy effects of olive oil consumption, such as prevention of unwanted aging processes. To date, there are no specific studies on the action of olive oil on MSCs, but effects of many components of such food on cell viability and differentiation have been evaluated. The objective of this article is to review existing literature on how different compounds of extra virgin olive oil, including residues of fatty acids, vitamins, squalene, triterpenes, pigments and phenols, affect MSC maintenance and differentiation, in order to provide a better understanding of the healthy effects of this food. Interestingly, most studies have shown a positive effect of these compounds on MSCs. The collective findings support the hypothesis that at least part of the beneficial effects of extra virgin olive oil consumption on health may be mediated by its effects on MSCs.

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Tracking and Imaging of Transplanted Stem Cells in Animals.

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Abstract

The shortage of organ donors has contributed to the rapid development of cell-based therapy in which stem cells are transplanted and administered to repair or regenerate damaged tissues or organs. The common sources of stem cells are embryonic, mesenchymal, stromal, and induced pluripotent cells.

Despite the popularity of stem cell therapy, evaluation of the therapeutic efficiency of transplanted stem cells and their tracking in vivo remains a major challenge. Current imaging modalities such as magnetic resonance imaging, radionuclide imaging, and positron emission tomography have certain limitations such as toxicity, shorter circulation time, and higher cost. Here, we describe near-infrared imaging methods to track and monitor stem cell recruitment to the site of injury.