ML20-20 (25/05/2020)

Bone 2020 May 20;115440.
doi: 10.1016/j.bone.2020.115440. Online ahead of print.

The Changing Epigenetic Landscape of Mesenchymal Stem/Stromal Cells During Aging

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- PMID: 32445894

- DOI: 10.1016/j.bone.2020.115440

Abstract

There is mounting evidence in the literature that mesenchymal stromal/stem cell (MSC) like populations derived from different tissues, undergo epigenetic changes during aging, leading to compromised connective tissue integrity and function. This body of work has linked the biological aging of MSC to changes in their epigenetic signatures affecting growth, lifespan, self-renewal and multi-potential, due to deregulation of processes such as cellular senescence, oxidative stress, DNA damage, telomere shortening and DNA damage. This review addresses recent findings examining DNA methylation, histone modifications and miRNA changes in aging MSC populations. Moreover, we explore how epigenetic factors alter cellular pathways and associated biological networks, contributing to the MSC aging phenotype. Finally we discuss the crucial areas requiring a greater understanding of these processes, in order to piece together a global picture of the changing epigenetic landscape in MSC during aging.

Cells 2020 May 20;9(5):E1268.
doi: 10.3390/cells9051268.

Tendon and Cytokine Marker Expression by Human Bone Marrow Mesenchymal Stem Cells in a Hyaluronate/Poly-Lactic-Co-Glycolic

Acid (PLGA)/Fibrin Three-Dimensional (3D) Scaffold

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- PMID: 32443833

- DOI: 10.3390/cells9051268

Abstract

We developed a (three-dimensional) 3D scaffold, we named HY-FIB, incorporating a force-transmission band of braided hyaluronate embedded in a cell localizing fibrin hydrogel and poly-lactic-co-glycolic acid (PLGA) nanocarriers as transient components for growth factor controlled delivery. The tenogenic supporting capacity of HY-FIB on human-Bone Marrow Mesenchymal Stem Cells (hBM-MSCs) was explored under static conditions and under bioreactor-induced cyclic strain conditions. HY-FIB elasticity enabled to deliver a mean shear stress of 0.09 Pa for 4 h/day. Tendon and cytokine marker expression by hBM-MSCs were studied. Results: hBM-MSCs embedded in HY-FIB and subjected to mechanical stimulation, resulted in a typical tenogenic phenotype, as indicated by type 1 Collagen fiber immunofluorescence. RT-qPCR showed an increase of type 1 Collagen, scleraxis, and decorin gene expression (3-fold, 1600-fold, and 3-fold, respectively, at day 11) in dynamic conditions. Cells also showed pro-inflammatory (IL-6, TNF, IL-12A, IL-1β) and anti-inflammatory (IL-10, TGF-β1) cytokine gene expressions, with a significant increase of anti-inflammatory cytokines in dynamic conditions (IL-10 and TGF-β1 300-fold and 4-fold, respectively, at day 11). Mechanical signaling, conveyed by HY-FIB to hBM-MSCs, promoted tenogenic gene markers expression and a pro-repair cytokine balance. The results provide strong evidence in support of the HY-FIB system and its interaction with cells and its potential for use as a predictive in vitro model.

J Tissue Eng Regen Med. 2020 May 22.
doi: 10.1002/term.3070. Online ahead of print.

An Easy Long-acting BMP7 Release System Based on Biopolymer Nanoparticles for Inducing Osteogenic

Differentiation of Adipose Mesenchymal Stem Cells

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- PMID: 32441466

- DOI: 10.1002/term.3070

Abstract

In contrast to the early acting bone morphogenetic protein 2 (BMP2), bone morphogenetic protein 7 (BMP7) plays a decisive role mainly in the late stages of bone formation. To overcome deactivation and degradation of expensive BMP7, we designed a novel long-acting BMP7 release system based on poly(3-hydroxybutyrate-co-4-hydroxybutyrate) (P34HB) nanoparticles to enable the induction of osteogenic differentiation in human adipose mesenchymal stem cells (ADSCs). In order to improve the encapsulation efficiency of BMP7 and avoid damage by organic solvents, BMP7 was modified and protected using the biosurfactant soybean lecithin. In an in-vitro test, BMP7-soybean lecithin-P34HB nanoparticles (BMP7-SPNPs) showed a short initial burst of BMP7 release during the first 24 h, followed by a steady increase to a cumulative 80% release in 20 days. Compared to the rapid release of control BMP7-PNPs loaded with BMP7 without soybean lecithin, BMP7-SPNPs significantly reduced the initial burst of BMP7 release and stabilized the content of BMP7 to allow long-term osteogenic differentiation during the late phase of bone development. Human ADSCs treated with BMP7-SPNPs showed higher ALP activity and higher expression levels of genetic markers of osteogenic differentiation compared to the control group. Thus, the results indicate that BMP7-SPNPs can be used as a rapid and long-acting BMP7 delivery system for osteogenic differentiation.

Adv Healthc Mater. 2020 May 19;e2000470.
doi: 10.1002/adhm.202000470. Online ahead of print.

Photoactive Interfaces for Spatio-Temporal Guidance of Mesenchymal Stem Cell Fate

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- PMID: 32431096

- DOI: 10.1002/adhm.202000470

Abstract

Patterned surfaces have proved effective in guiding stem cells commitment to a specific lineage by presenting highly ordered biophysical/biochemical cues at the cellmaterial interface. Their potency in controlling cell fate can be significantly empowered by encoding logic of space and time control of signal presentation. Here, azopolymeric photoactive interfaces are proposed to present/withdraw morphophysical signals to living cells using a green light trigger in a non-invasive spatio-temporal controlled way. To assess the potency of these dynamic platforms in controlling cell decision and fate, topography changes are actuated by light at specific times to reverse the fate of otherwise committed human mesenchymal stem cells (hMSC) toward osteoblastic lineage. It is first proved by dynamic change from ordered parallel patterning to flat or grid surfaces, that it is possible to induce cyclic cellular and nuclear stretches. Furthermore, by culturing hMSCs on a specific pattern known to prime them toward osteoblast lineage, the possibility to reroute or reverse stem cell fate decision by dynamic modulation of morphophysical signal is proved. To conclude, dynamic topographies can control the spatial conformation of hMSCs, modulate lineage reversal even after several weeks of culture and redirect lineage specification in response to light-induced changes in the microenvironment.

ACS Appl Mater Interfaces. 2020 May 18.
doi: 10.1021/acsami.0c05012. Online ahead of print.

Synergistic Effect of Cell-Derived Extracellular Matrix and Topography on Osteogenesis of Mesenchymal Stem Cells

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- PMID: 32423202

- DOI: 10.1021/acsami.0c05012

Abstract

Cell-derived matrices (CDM) are an interesting alternative to the conventional sources of extracellular matix (ECM) as CDM mimics better the natural ECM composition and are therefore attractive as a scaffolding material to be used for regulating the functions of stem cells. Previous research on stem cell differentiation has demonstrated that both surface topography and CDM have a significant influence. However, not much focus has been placed on elucidating possible synergistic effects of CDM and topography on osteogenic differentiation of human bone marrow-derived mesenchymal stem cells (hBM-MSCs). In this study, Polydimethylsiloxane (PDMS)-based anisotropic topographies (wrinkles) with various topography dimensions were prepared and subsequently combined with native ECM produced by human fibroblasts that remained onto the surface topography after decellularization. The synergistic effect of CDM combined with topography on osteogenic differentiation of hBM-MSCs was investigated. The results showed that substrates with specific topography dimensions, coated with aligned CDM, dramatically enhanced the capacity of osteogenesis as investigated using immunofluorescent staining for identifying osteopontin (OPN) and mineralization. Furthermore, the hBM-MSCs on the substrates decorated with CDM exhibited higher percentage of YAP inside the nucleus, stronger cell contractility, and more formation of focal adhesion, illustrating that enhanced osteogenesis is partly mediated by cellular tension and mechanotransduction following the YAP pathway. Taken together, our findings highlight the importance of ECM mediating the osteogenic differentiation of stem cells, and the combination of CDM and topography will be a powerful approach for material-driven osteogenesis.

Stem Cell Rev Rep. 2020 May 16.
doi: 10.1007/s12015-020-09974-9. Online ahead of print.

Aging-Related Reduced Expression of CXCR4 on Bone Marrow Mesenchymal Stromal Cells Contributes to Hematopoietic Stem and Progenitor Cell Defects

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- PMID: 32418119

- DOI: 10.1007/s12015-020-09974-9

Abstract

Aging impairs the regenerative potential of hematopoietic stem cells (HSC) and skews differentiation towards the myeloid lineage. The bone marrow (BM) microenvironment has recently been suggested to influence HSC aging, however the mechanisms whereby BM stromal cells mediate this effect is unknown. Here we show that aging-associated decreased expression of CXCR4 expression on BM mesenchymal stem cells (MSC) plays a crucial role in the development of the hematopoietic stem and progenitor cells (HSPC) aging phenotype. The BM MSC from old mice was sufficient to drive a premature aging phenotype of young HSPC when cultured together ex vivo. The impaired ability of old MSC to support HSPC function is associated with reduced expression of CXCR4 on BM MSC of old mice. Deletion of the CXCR4 gene in young MSC accelerates an aging phenotype in these cells characterized by increased production of reactive oxygen species (ROS), DNA damage, senescence, and reduced proliferation. Culture of HSPC from young mice with CXCR4 deficient MSC also from young mice led to a premature aging phenotype in the young HSPC, as evidenced by reduced hematopoietic regeneration and enhanced myeloid differentiation. Mechanistically, CXCR4 signaling prevents BM MSC dysfunction by suppressing oxidative stress, as treatment of old or CXCR4 deficient MSC with N-acetyl-L-cysteine (NAC), improved their niche supporting activity, and attenuated the HSPC aging phenotype. Our studies suggest that age-associated reduction in CXCR4 expression on BM MSC impairs hematopoietic niche activity with increased ROS production, driving an HSC aging phenotype. Thus, modulation of the SDF-1/CXCR4 axis in MSC may lead to novel interventions to alleviate the age-associated decline in immune/hematopoietic function.