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ECM scaffolds mimicking extracellular matrices of endochondral ossification for the regulation of mesenchymal stem cell differentiation

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Abstract

Endochondral ossification (ECO) is an important process of bone tissue development. During ECO, extracellular matrices (ECMs) are essential factors to control cell functions and induce bone regeneration. However, the exact role of ECO ECMs on stem cell differentiation remains elusive. In this study, ECM scaffolds were prepared to mimic the ECO-related ECM microenvironments and their effects on stem cell differentiation were compared. Four types of ECM scaffolds mimicking the ECMs of stem cells (SC), chondrogenic (CH), hypertrophic (HY) and osteogenic (OS) stages were prepared by controlling differentiation of human bone marrow-derived mesenchymal stem cells (MSCs) at different stages. Composition of the ECM scaffolds was dependent on the differentiation stage of MSCs. They showed different influence on osteogenic differentiation of MSCs. HY-ECM scaffold had the most promotive effect on osteogenic differentiation of MSCs. CH ECM and OS ECM scaffolds showed moderate effect, while SC ECM scaffold had the lowest effect on osteogenic differentiation of MSCs. Their effects on chondrogenic or adipogenic differentiation were not significantly different. The results suggested that the engineered HY ECM scaffold had superior effect for osteogenic differentiation of MSCs. Statement of significance ECM scaffolds mimicking endochondral ossification-related ECM microenvironments are pivotal for elucidation of their roles in regulation of stem cell functions and bone tissue regeneration. This study offers a method to prepare ECM scaffolds that mimic the ECMs from cells at hypertrophic, osteogenic, chondrogenic and

stem cell stages. Their composition and impacts on osteogenic differentiation of MSCs were compared. The hypertrophic ECM scaffold had the highest promotive effect on osteogenic differentiation of MSCs. The results advance our understanding about the role of ECO ECMs in regulation of stem cell functions and provide perspective for bone defect repair strategies.

Cytotherapy

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Regulatory-compliant conditions during cell product manufacturing enhance in vitro immunomodulatory properties of infrapatellar fat pad-derived mesenchymal stem/stromal cells

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Abstract

Background aims: Mesenchymal stem/stromal cell (MSC)-based therapies have gained attention as potential alternatives for multiple musculoskeletal indications based on their trophic and immunomodulatory properties. The infrapatellar fat pad (IFP) serves as a reservoir of MSCs, which play crucial roles modulating inflammatory and fibrotic events at the IFP and its neighboring tissue, the synovium. In an effort to comply with the existing regulatory framework regarding cell-based product manufacturing, we interrogated the in vitro immunomodulatory capacity of human-derived IFP-MSCs processed under different conditions, including a regulatory-compliant protocol, in addition to their response to the inflammatory and fibrotic environments often present in joint disease.

Methods: Immunophenotype, telomere length, transcriptional and secretory immunomodulatory profiles and functional immunopotency assay were assessed in IFP-MSCs expanded in regular fetal bovine serum (FBS)-supplemented medium and side-by-side compared with same-donor cells processed with two media alternatives (i.e., regulatory-compliant pooled human platelet lysate [hPL] and a chemically reinforced/serum-reduced [Ch-R] formulation). Finally, to assess the effects of such formulations on the ability of the cells to respond to pro-inflammatory and pro-fibrotic conditions, all three groups were stimulated ex vivo (i.e., cell priming) with a cocktail containing TNFα, IFNγ and connective tissue growth factor (tumor-initiating cells) and compared with non-induced cohorts assessing the same outcomes.

Results: Non-induced and primed IFP-MSCs expanded in either hPL or Ch-R showed distinct morphology in vitro, similar telomere dynamics and distinct phenotypical and molecular profiles when compared with cohorts grown in FBS. Gene expression of IL-8, CD10 and granulocyte colony-stimulating factor was highly enriched in similarly processed IFP-MSCs. Cell surface markers related to the immunomodulatory capacity, including CD146 and CD10, were highly expressed, and secretion of immunomodulatory and pro-angiogenic factors was significantly enhanced with both hPL and Ch-R formulations. Upon priming, the immunomodulatory phenotype was enhanced, resulting in further increase in CD146 and CD10, significant CXCR4 presence and reduction in TLR3. Similarly, transcriptional and secretory profiles were enriched and more pronounced in IFP-MSCs expanded in either hPL or Ch-R, suggesting a synergistic effect between these formulations and inflammatory/fibrotic priming conditions. Collectively, increased indoleamine-2,3-dioxygenase activity and prostaglandin E2 secretion for hPL- and Ch-R-expanded IFP-MSCs were functionally reflected by their robust T-cell proliferation suppression capacity in vitro compared with IFP-MSCs expanded in FBS, even after priming.

Conclusions: Compared with processing using an FBS-supplemented medium, processing IFP-MSCs with either hPL or Ch-R similarly enhances their immunomodulatory properties, which are further increased after exposure to an inflammatory/fibrotic priming environment. This evidence supports the adoption of regulatory-compliant practices during the manufacturing of a cell-based product based on IFP-MSCs and anticipates a further enhanced response once the cells face the pathological environment after intra-articular administration. Mechanistically, the resulting functionally enhanced cell-based product has potential utilization as a novel, minimally invasive cell therapy for joint disease through modulation of local immune and inflammatory events.

Keywords: cell product manufacturing; cell therapy; human platelet lysate; immunomodulation; infrapatellar fat pad; mesenchymal stem/stromal cells

Cell Death Differ

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Intranasal delivery of mesenchymal stem cell secretome repairs the brain of Alzheimer's mice

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Abstract

The multiplicity of systems affected in Alzheimer's disease (AD) brains calls for multi-target therapies. Although mesenchymal stem cells (MSC) are promising candidates, their clinical application is limited because of risks related to their direct implantation in the host. This could be overcome by exploiting their paracrine action. We herein demonstrate that in vivo systemic administration of secretome collected from MSC exposed in vitro to AD mouse brain homogenates (MSC-CS), fully replicates the cell-mediated neuroreparative effects in APP/PS1 AD mice. We found a complete but transient memory recovery by 7 days, which vanished by 14 days, after a single MSC-CS intravenous administration in 12-month or 22-24-month-old mice. Treatment significantly reduced plaque load, microglia activation, and expression of cytokines in astrocytes in younger, but not aged, mice at 7 days. To optimize efficacy, we established a sustained treatment protocol in aged mice through intranasal route. Once-weekly intranasal administration of MSC-CS induced persistent memory recovery, with dramatic reduction of plaques surrounded by a lower density of β-amyloid oligomers. Gliosis and the phagocytic marker CD68 were decreased. We found a higher neuronal density in cortex and hippocampus, associated with a reduction in hippocampal shrinkage and a longer lifespan indicating healthier conditions of MSC-CS-treated compared to vehicle-treated APP/PS1 mice. Our data prove that MSC-CS displays a great multi-level therapeutic potential, and lay the foundation for identifying the therapeutic secretome bioreactors leading to the development of an efficacious multi-reparative cocktail drug, towards abrogating the need for MSC implantation and risks related to their direct use.