



Control/Tracking Number: 13-A-711-OARSI

Activity: Abstract

Current Date/Time: 12/3/2012 5:06:32 PM

FIBROBLAST GROWTH FACTOR -1 IS A MESENCHYMAL STROMAL CELL SECRETED FACTOR
STIMULATING PROLIFERATION OF OSTEOARTHRITIC CHONDROCYTES

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Abstract:

Purpose: Intra-articular injection of human mesenchymal stromal cells (MSCs) is currently under investigation for disease modifying treatment of osteoarthritis. In vitro experiments have shown beneficial effects of MSCs on chondrocytes in a variety of co-culture models in terms of cartilage matrix formation. We have shown that in pellet co-cultures this beneficial effect with respect of cartilaginous matrix formation is predominantly due to stimulation of chondrocyte proliferation by the MSCs rather than to chondrogenic differentiation of the MSCs themselves. In addition, we have shown that this beneficial effect on chondrocyte proliferation in pellet cultures is mainly due to the secretion of (a) soluble factor(s) by the MSCs. The objective of this study is to identify this factor(s) which may be (an) important mediator(s) of the disease modifying trophic role of MSCs in osteoarthritis.

Methods:

Human primary chondrocytes (hPCs) isolated from late stage osteoarthritis patients were used in pellet co-culture with human bone marrow derived MSCs (hMSCs). DNA microarray experiments were performed to investigate the gene expression profiles of co-culture and mono-culture pellets (hPCs or hMSCs respectively). Quantitative polymerase chain reaction (qPCR) and species specific PCR in co-culture pellets of hMSCs and bovine PCs were carried out to validate microarray data. Immunofluorescent staining combined with cell tracking and Enzyme-linked immunosorbent assay (ELISA) were performed to confirm the expression of candidate genes at the protein level. Chemical blockers and neutralizing antibodies were used to study the functions of candidate genes in co-cultures.

Results:

Microarray data revealed a number of candidate secreted soluble factors. Of these, Fibroblast Growth Factor-1 (FGF-1) mRNA expression was markedly increased in co-culture pellets. Species specific PCR in xenogenic co-culture pellets of bovine PCs and MSCs confirmed the upregulation of Fgf1 mRNA in the MSCs. Immunofluorescent staining in combination with cell tracking experiments confirmed the up-regulation of FGF-1 in co-culture pellets particularly in the MSC cell fraction. Interestingly, FGF-1 expression was highest in MSCs in direct contact with hPCs. ELISA demonstrated increased FGF-1 secretion in medium of pellet co-cultures only. Interestingly, blocking of FGF

signaling in co-culture pellets by specific FGF receptor inhibitors or FGF-1 neutralizing antibodies completely abolished chondrocyte proliferation. Likewise, neutralizing FGF-1 activity in MSC conditioned medium by anti-FGF-1 antibodies also completely blocked chondrocyte proliferation.

Conclusions:

We demonstrate that MSCs increase FGF-1 secretion upon co-culture with chondrocytes, which in turn is responsible for increased chondrocyte proliferation in these co-culture pellets. Our study identifies FGF-1 as a potent trophic mediator of the proposed beneficial effects of intra-articular injected MSCs in the osteoarthritic joint which may contribute to cartilage regeneration.

Category (Complete): Regenerative medicine

Keyword (Complete): Mesenchymal Stem Cell ; Chondrogenesis ; Fibroblastic Growth Factor- B ; Tissue Engineering

Presentation Preference (Complete): Podium Preference

Type of Abstract (Required): Basic Science

Status: Complete

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