

Synergistic Effect of Chondroinductive Growth Factors and Synovium-Derived Mesenchymal Stem Cells on Regeneration of Cartilage Defects in Rabbits

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Abstract : Regeneration of injured articular cartilage remains one of the most difficult and unsolved problems in traumatology and orthopedics. Currently, for the treatment of cartilage defects surgical techniques for stimulation of the regeneration of cartilage in damaged joints such as multiple microperforation, mosaic chondroplasty, abrasion and microfractures is used. However, as shown by clinical practice, they can not provide a full and sustainable recovery of articular hyaline cartilage. In this regard, the current high hopes in the regeneration of cartilage defects reasonably are associated with the use of tissue engineering approaches to restore the structural and functional characteristics of damaged joints using stem cells, growth factors and biopolymers or scaffolds. The purpose of the present study was to investigate the effects of chondroinductive growth factors and synovium-derived mesenchymal stem cells (SD-MSCs) on the regeneration of cartilage defects in rabbits. SD-MSCs were isolated from the synovium membrane of Flemish giant rabbits, and expanded in complete culture medium α -MEM. Rabbit SD-MSCs were characterized by CFU-assay and by their ability to differentiate into osteoblasts, chondrocytes and adipocytes. The effects of growth factors (TGF- β 1, BMP-2, BMP-4 and IGF-I) on MSC chondrogenesis were examined in micromass pellet cultures using histological and biochemical analysis. Articular cartilage defect (4mm in diameter) in the intercondylar groove of the patellofemoral joint was performed with a kit for the mosaic chondroplasty. The defect was made until subchondral bone plate. Delivery of SD-MSCs and growth factors was conducted in combination with hyaluronic acid (HA). SD-MSCs, growth factors and control groups were compared macroscopically and histologically at 10, 30, 60 and 90 days after intra-articular injection. Our in vitro comparative study revealed that TGF- β 1 and BMP-4 are key chondroinductive factors for both the growth and chondrogenesis of SD-MSCs. The highest effect on MSC chondrogenesis was observed with the synergistic interaction of TGF- β 1 and BMP-4. In addition, biochemical analysis of the chondrogenic micromass pellets also revealed that the levels of glycosaminoglycans and DNA after combined treatment with TGF- β 1 and BMP-4 was significantly higher in comparison to individual application of these factors. In vivo study showed that for complete regeneration of cartilage defects with intra-articular injection of SD-MSCs with HA takes time 90 days. However, single injection of SD-MSCs in combination with TGF- β 1, BMP-4 and HA significantly promoted regeneration rate of the cartilage defects in rabbits. In this case, complete regeneration of cartilage defects was observed in 30 days after intra-articular injection. Thus, our in vitro and in vivo study demonstrated that combined application of rabbit SD-MSC with chondroinductive growth factors and HA results in strong synergistic effect on the chondrogenesis significantly enhancing regeneration of the damaged cartilage.

Keywords : Mesenchymal stem cells, synovium, chondroinductive factors, TGF- β 1, BMP-2, BMP-4, IGF-I

Conference Title : ICSCRM 2015 : International Conference on Stem Cells and Regenerative Medicine

Conference Location : London, United Kingdom

Conference Dates : September 25-26, 2015