Sustained Release of Bone Morphogenetic Protein 2 via Coacervate: A Novel Tissue Engineered Approach for Osteoarthritis Treatment

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Introduction/Purpose: Currently, there is no cure for osteoarthritis (OA) with treatment aimed at symptom relief and improved function. Muscle-derived stem cells (MDSCs) have been shown to exhibit long-term proliferation, high self-renewal, and can undergo chondrogenic differentiation when cultivated in chondrogenic medium in vitro and can differentiate into chondrocytes and repair injured articular cartilage (AC) in vivo. MDSCs retrovirally transduce to express chondrogenic proteins (BMPs) to differentiate into chondrocytes and enhance cartilage repair in vivo. Gene therapy is a promising approach to promote the chondrogenic potentials of MDSCs for AC repair. We have developed a unique sustained growth factor delivery platform comprised of native heparin and a synthetic polycation incorporated with BMP2 (BMP2 coacervate) which can sustain delivery of BMPs to stimulate the chondrogenesis of MDSCs for AC repair.

Methods: MDSC were stimulated in vitro with single dose of free BMP2, multi-dose BMP2, BMP2 coacervate, coacervate alone (vehicle only), or in the absence of BMP2 and coacervate (control). BMP2 effects on MDSCs were evaluated by RT-PCR. 20µl of a MIA solution was injected into the knee joint of C57B6 mice to induce osteoarthritic lesions. Two weeks after MIA injection, 20µl of PBS (PBS control), 1×106 MDSCs with 1µg of free BMP2 (MDSC-free BMP), or MDSCs with 1µg BMP2-coacervate (MDSC-BMP coacervate) were injected into the knee joints of the OA injured mice. After 4 weeks, macroscopic and histologic evaluations of cartilage regeneration were conducted.

Results: mRNA expression of Aggrecan and Col2A were significantly higher in each BMP2 group compared to control or vehicle only ($P < 0.05$). Multi-dosage free BMP2 demonstrated significantly higher Aggrecan expression compared to single dose free BMP2 ($p < 0.05$). Col2A and aggrecan expression in the BMP coacervate group was superior to both single and mult-dose free BMP2 delivery ($p < 0.05$) (Fig 1A). Histologic examination demonstrated superior cartilage repair and integration in the BMP2 coacervate group (Fig. 1B).

Conclusion: This study demonstrates that sustained growth factor delivery (BMP2) is a potential therapeutic option for muscle-derived stem cell based cartilage regeneration for the treatment of osteoarthritis. Prolonged delivery of BMP2 via coacervate led to enhanced MDSC chondrogenesis in vivo and improved cartilage regeneration in vivo. Our results demonstrate an effective method for prolonged exposure to BMP2 and is more clinically translatable.

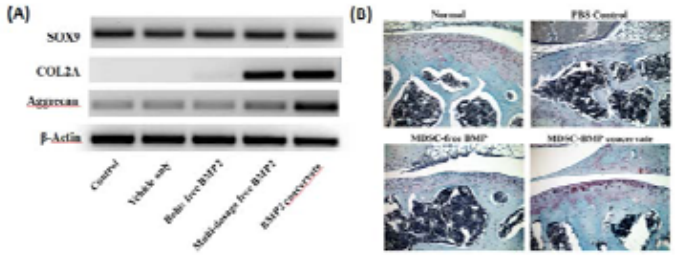

Figure 1. (A) *In vitro* MDSCs chondrogenesis following BMP2 delivery via RT-PCR; (B) Histological analysis of cartilage regeneration in MIA-induced OA via Safranin-O staining.

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