The Effects of Intra-Articular Treatment with Recombinant Human Bone Morphogenetic Protein 7 (rhBMP-7) on the Development of Post-Traumatic Osteoarthritis in Surgically Induced Rat Models

Introduction

Several experimental animal models have been developed for human osteoarthritis (OA) and used to study the preclinical efficacy of disease and symptom modifying OA drug candidates in various species.1-7 One of these drug candidates is recombinant human bone morphogenetic protein 7 (rhBMP-7).8 It is a bone-inducing agent used currently in clinical practice to enhance bone formation in spinal fusions and during fracture repair. In preclinical studies, intra-articular rhBMP-7 treatment has been shown to attenuate the development of degenerative changes induced by anterior cruciate ligament transection (ACLTr) in rabbits and by excessive running in rats and to repair cartilage damage in rabbits, goats, sheep and dogs.

In this study, we characterized the effects of intra-articular rhBMP-7 treatment on the development of post-traumatic OA in surgically induced rat models.

Materials and Methods

Articular expression of rhBMP-7 in surgically induced rat models: Three rat ACLT models, one static and two post-traumatic, were used in this study: Rat ACLT Model, Rat MMT + MCLT Model, and Rat MMT + MCLT Model. Treatment was divided into four groups for each model: Control (Vehicle), rhBMP-7 treatment, rhBMP-7 treatment, and rhBMP-7 treatment.

Surgical Induction of Post-Traumatic OA Models

Rat ACLT Model: This model was developed by starting the MCL and MMT ligaments in both knees of male Sprague-Dawley rats at 3 weeks of age.2,3 In this model, the rats were operated at 4 weeks of age.3

Rat MMT + MCLT Model: This model was developed by starting the MCL ligament in one knee and the MMT ligament in the other knee of male Sprague-Dawley rats at 3 weeks of age.2,3 In this model, the rats were operated at 4 weeks of age.3

Histological and biochemical analyses were performed on formalin-fixed tissues stained for Toluidine blue, Masson’s trichrome, and picrosirius red.

Results

Summary

Knee joint discomfort and pain were observed together with a reduction in body weight in all rat OA models at the start of treatment.

Rat MMT + MCLT model demonstrated knee joint discomfort/pain also at 3 weeks, and knee joint discomfort, cartilage degeneration and the loss of extracellular matrix (ECM) down to tidemark, large osteophytes and synovial inflammation at 6 weeks post-surgery.

Intra-articular treatment with rhBMP-7 improved knee joint discomfort and pain at 3 weeks, and attenuated the cartilage degeneration and the loss of ECM focally at 6 weeks post-surgery.

Rat ACLT + rhBMP-7 model exhibited knee joint pain also at 4 weeks, and knee joint pain, cartilage degeneration and ECM loss down to tidemark, moderate osteophytes and synovial inflammation at 8 weeks post-surgery.

Intra-articular treatment with rhBMP-7 attenuated the cartilage degeneration focally in superficial layer at 8 weeks post-surgery.

Rat ACLT model demonstrated knee joint discomfort and pain also at 5 weeks, and cartilage degeneration and the loss of ECM down to deep layer, moderate osteophytes and synovial inflammation at 10 weeks post-surgery.

Intra-articular treatment with rhBMP-7 improved knee joint discomfort at 5 weeks and attenuated the loss of ECM focally at 10 weeks post-surgery.

Conclusions

This study demonstrated a minor chondroprotective activity for intra-articular treatment with rhBMP-7 in three rat models of post-traumatic OA.

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References