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ORIGINAL ARTICLE

Translational potential of ginsenoside Rb1 in managing progression of osteoarthritis

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KEYWORDS
cartilage;
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Summary *Background:* Osteoarthritis (OA) is the most common degenerative joint disorder. Inflammatory cytokine plays an important role in OA progression. Previous studies have demonstrated that ginsenoside Rb1 would prevent inflammation and apoptosis in chondrocytes. However, we have not found any animal study reporting that Rb1 attenuates the severity of OA.
Objective: In this study, we used a rat anterior cruciate ligament transaction plus medial meniscus resection (ACLT + MMx) model of OA and a cell model, to investigate whether administration of ginsenoside Rb1 may attenuate the progression of arthritis.
Methods: In this *in vivo* study, 16-week-old male Sprague—Dawley rats were divided into three groups: Group 1 (sham control group), Group 2 (Rb1-treated group), and Group 3 (OA group). In Groups 2 and 3, OA was induced in the right knee joint with ACLT + MMx in rats. Then Group 2 received continuous infusion of ginsenoside Rb1 via osmotic mini-pumps implanted subcutaneously. At 4 weeks after treatment, the rats were sacrificed. Interleukin-1β (IL-1β) level was evaluated by enzyme-linked immunosorbent assay (ELISA); cartilage damage was assessed via histology (Safranin-O/fast green stain) and immunohistochemistry [matrix metalloproteinase-13 (MMP13) and type X collagen (Col X)]. For cell study, C5.18 (rat chondrocyte cell line) was used in this research. The effect of Rb1 on IL-1β-induced MMP13 or Col X

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expression level in C5.18 cells was investigated.
Results: In this *in vivo* study, characteristics of OA were present in the OA group, in contrast to less severe damage generally observed in the Rb1 treatment group: first, IL-1β level was significantly decreased, and second, cartilage degeneration was attenuated, as indicated by lower histologic damage scores and lower percentages of MMP13 or Col X-positive chondrocytes. In the cell study, the results showed that Rb1 treatment would relieve the MMP13 or Col X expression in C5.18 cells induced by IL-1β.
Conclusion: In the present study, we demonstrated that Rb1 can attenuate the progression or severity of arthritis by reducing inflammation.
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Introduction

Osteoarthritis (OA) is one of the most common progressive joint disorders affecting our elderly population. The condition is pathologically characterized by cartilage degeneration, changes in subchondral bone matrix, and secondary synovial inflammation. Clinical presentation comprises pain, joint stiffness, and declining activity of daily functions [1—3]. Inflammatory cytokine plays an important role in OA progression [4—8]. For example, studies have shown that these inflammatory cytokines, including interleukin-1β (IL-1β) and stromal cell-derived-factor 1, are involved in lubricin catabolism and cartilage degeneration. Their mechanism resides in the upregulation of matrix metalloproteinase-13 (MMP13) that has been shown to cleave type II collagen and proteoglycans [5—8]. In addition, they can further inhibit the synthesis of the main constituents of the extracellular matrix, type II collagen, and aggrecan. These factors lead to the disruption of the normal articular cartilage homeostasis and the eventual breakdown of cartilage in OA.

Current research and treatment focus on identifying a method to regulate this mechanism, and thus, prevent or delay the breakdown of the articular cartilage or regenerate it. A class of natural products such as steroid glycosides and triterpene saponins, known as ginsenosides, has been identified as the principal active components in pharmacological studies of ginseng [9]. At the present time, over 40 ginsenosides have been identified, which show different biological activities based on structural differences. The most abundant ginsenoside Rb1 has been shown to have a variety of biological activities, including anti-inflammatory, antiapoptotic, and neuroprotective activities [10,11]. Previous *in vitro* studies have demonstrated that Rb1 would prevent IL-1β- or hydrogen peroxide (H_2O_2)-induced inflammation and apoptosis in chondrocytes [12,13]. In an *in vivo* study, Endale et al [14] proved that Rb1 would attenuate the severity of mouse collagen-induced arthritis. However, the effect of ginsenosides in a degenerative animal model remains unexplored.

The objective of this study is to investigate whether systemic administration of ginsenoside Rb1 may attenuate OA progression in a severe post-traumatic rat arthritis model.

Materials and methods

Animal surgery

All experiments were approved by the Animal Research Ethics Committee of the Chinese University of Hong Kong. In this study, 16-week-old male Sprague—Dawley rats, weighing 450—500 g, were used. The animals were allocated randomly into three groups. Group 1 involved an open arthrotomy and sutured closure, this served as the sham control ($n = 5$). In Groups 2 and 3, the rats were subjected to the anterior cruciate ligament transaction plus medial meniscus resection (ACLT + MMx) as described previously [15]. In brief, each rat was anaesthetized with a solution of 0.2% (vol/vol) xylazine and 1% (vol/vol) ketamine in phosphate-buffered saline (PBS), and after being shaved and disinfected, the right knee joint was exposed through a medial parapatellar arthrotomy approach. The patella was dislocated laterally and the knee was placed in full flexion, followed by anterior cruciate ligament (ACL) and medial cruciate ligament (MCL) transection with microscissors and resection of the medial meniscus. Group 2 is the Rb1-treated group; rats of this group received continuous infusion of ginsenoside Rb1 (PI & PI Technology Inc., Guangzhou, China) via osmotic mini-pumps ($n = 5$); The osmotic mini-pumps (model 2006; Alza Corporation, Mountain View, CA, USA) were inserted into small subcutaneous pockets over the dorsolateral thorax, created by blunt dissection after a small incision (~1 cm). Prior to insertion, 200-μL pump reservoirs were filled with Rb1 (300μM) dissolved in pure ethanol. The average pumping rate of the mini-osmotic pumps is 0.15 μL/h. Group 3 rats were left untreated and used as the OA controls ($n = 5$). In accordance with our animal ethics protocol, all the animal surgical procedures were performed under general anaesthesia and analgesic medications. After 4 weeks of treatment, all animals were euthanized, and then the right knees of animals were aspirated for analysis.

Blood collection and serum analysis

Blood (5 mL) was collected by cardiac puncture immediately after the animals were killed. The blood was centrifuged at 1800*g* for 10 minutes, and the separated serum

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