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Treatment with recombinant lubricin attenuates osteoarthritis by positive feedback loop between articular cartilage and subchondral bone in ovariectomized rats ☆

Zhuang Cui, Changpeng Xu, Xue Li, Jinqi Song, Bin Yu *

Orthopedics and Traumatology, NanFang hospital, Southern Medical University, No. 1838 Guangzhou Da Dao Bei, Guangzhou, Guangdong Province 510515, China

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ABSTRACT

Osteoarthritis (OA) is a most commonly multifactorial degenerative joint disease along with the aging population, particularly in postmenopausal women. During the onset of OA, articular cartilage and subchondral bone act in concert as a functional unit. This present study is to investigate the effects of early or late treatment with recombinant lubricin on the onset of osteoarthritis (OA) in ovariectomized (OVX) rats. We found that both early and late recombinant lubricin treatments attenuated the onset of OA by positive feedback loop between articular cartilage and subchondral bone, although late treatment contributed to a lesser effect compared with early treatment. Specifically, treatment with recombinant lubricin protected articular cartilage from degeneration, demonstrated by lower proteoglycan loss, lower OARSI scores, less calcification cartilage zone and reduced immunostaining for collagen X (Col X) and matrix metalloproteinase (MMP-13) but increased the expression of lubricin, in comparison with vehicle-treated OVX rat group. Further, chondroprotective effects of lubricin normalized bone remodeling in subchondral bone underneath. It's suggested that treatment with recombinant lubricin inhibited the elevation of TRAP and Osterix positive cells in OVX rats and led to the normalization of subchondral bone microarchitectures with the suppression of subsidence of bone volume ratio (BV/TV) and trabecular thickness (Tb.Th) and the increase of trabecular separation (Tb.Sp) in vehicle-treated OVX rats. What's more, the normalization of subchondral bone in turn attenuated the articular cartilage erosion by inhibiting vascular invasion from subchondral bone to calcified cartilage zone, exemplified by inhibiting the elevation of CD31 positive cells in calcified cartilage and angiography in subchondral bone. Together, these results shed light that both early and late recombinant lubricin treatments attenuate the onset of OA by balancing the interplay between articular cartilage and subchondral bone in OVX rats, while also providing a further rationale for its therapeutic targeting to postmenopausal OA and suggesting that treatment timing is a pivotal factor for better effect acquisition.

Introduction

Osteoarthritis(OA) is a most commonly multifactorial degenerative joint disease and the major cause of physical disability [1], which is characterized by escalated cartilage loss, subchondral bone sclerosis and osteophyte formation [2–4]. Due to its incurable, costly and poor response to therapy, OA represents an enormous societal burden that elevates greatly along with the aging population. Generally, OA is divided into primary or secondary OA. Primary OA is considered as the spontaneously evolving OA such as post-menopausal OA, while secondary OA is deemed to be induced by some predisposing factors such as traumatic injury or administration of glucocorticoid [5]. Previous studies primarily focused on the secondary OA by using of anterior cruciate ligament transaction (ACLT) or glucocorticoid induced models, however, the results from secondary OA may not be applied to the primary OA, particularly in menopause-related OA as primary OA is evolved spontaneously. We expect to find some model which is able to mimic the pathophysiologic process of primary OA in menopause-related OA patients. Of note, recent studies revealed that older OVX rats are capable to be applied as an in vivo model for OP-related postmenopausal OA [6–8] and OVX enhances the severity of cartilage degeneration induced by ACTL [9]. In addition, several studies have demonstrated the correlation

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* Corresponding author. Fax: +86 20 61641888.
E-mail addresses: cuizhuang3816@163.com (Z. Cui), buzaiyouyu5945@163.com (C. Xu), 332478744@qq.com (X. Li), 360589376@qq.com (J. Song), cuizhuang5945@gmail.com (B. Yu).

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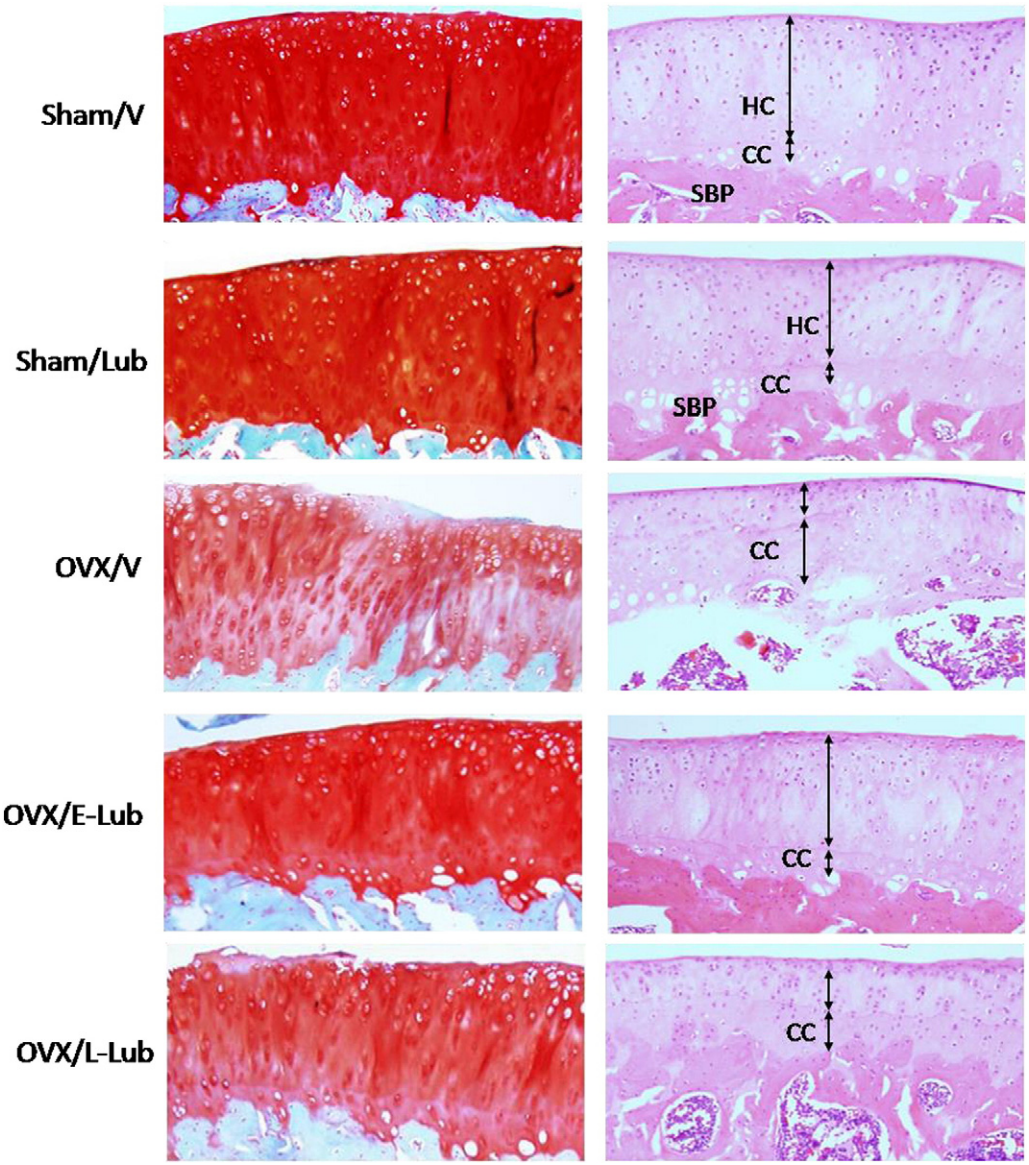

Fig. 1. Effect of recombinant lubricin on cartilage degeneration. Left column represents safranin O and fast green staining. Scale bar, 200 μm. Right column shows H&E staining and the calcified cartilage (CC) and hyaline cartilage (HC) thicknesses are marked by double-headed arrows. Scale bars, 200 μm. SBP: subchondral bone plate; CC: calcified cartilage; HC: hyaline cartilage (the cartilage from articular surface to tidemark line is set to hyaline cartilage, and that from tidemark line to subchondral bone plate (SBP) is calcified cartilage); Sham/V: vehicle treated sham; Sham/Lub: lubricin treated sham; OVX/E-lub: early lubricin treated OVX rats; OVX/L-lub: late lubricin treated OVX rats.

between osteoporosis (OP) and OA by the use of OVX animal model [10,11]. Therefore, OVX model is employed in our study to explore the effect of recombinant human lubricin on the onset of OA.

Articular cartilage, a stratified connective tissue that resided at the ends of long bones, plays a pivotal role in normal physical activities to bear weight load, reduce interarticular friction and resist the wear of the joints. The degradation of articular cartilage is a primary clinical problem in patients with osteoporosis due to its limited capability of self-repair [12,13]. The fate of cartilage greatly depends on the interplay between articular cartilage and subchondral bone underneath. Increasing evidence shows that articular cartilage and subchondral bone act in concert as a functional unit [14]. Subchondral bone provides mechanical support for overlying articular cartilage and undergoes constant adaption to respond to the changes in the mechanical environment by modeling and remodeling [15,16]. Recent studies have reported that bone resorption and formation, during bone remodeling, occur following a well-defined bone remodeling cycle and undergo at specific anatomical sites [17,18], while abnormal bone remodeling in subchondral bone induces overlying cartilage degeneration by recruiting mesenchymal stem cells (MSCs) to form aberrant bone marrow osteoid islets [19]. In turn, the maintenance of articular cartilage homeostasis and integrity might be able to lead to the alteration in articular load distribution and affect the bone remodeling of subchondral bone underneath.

Lubricin, also known as proteoglycan 4 (PRG4) or superficial zone protein (SZP), possesses a major chondroprotective role via the prevention of cartilage wear, synovial cell adhesion and proliferation [20]. Lubricin is a 227.5-kDa mucinous glycoprotein encoded by PRG4 gene [21], which was initially identified as a lubricating glycoprotein in synovial fluid [22]. Lubricin is secreted by various tissues such as superficial zone chondrocytes [23], synoviocytes [24], synovial fibroblasts [25], meniscal cells [26], tenocytes [27], infrapatellar fat pad (IFP) stromal cells [28] and anterior cruciate ligament (ACL)/lateral collateral ligament (LCL) cells [29]. Some studies have showed that the level of lubricin expression is down-regulated in various OA animal models such as sheep [30], guinea pig [31] and rat models