Delayed lubricin injection improves cartilage repair in an in vivo rabbit osteochondral defect model

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INTRODUCTION: High quality repair of osteochondral (OCL) defects in articular cartilage has been an enduring challenge. Previous studies have shown that lower interfacial strains and slopes correlate with better cartilage repair,[1] and that therapies that effectively lubricate the joint decrease shear strains and prevent cell death.[2] These data suggest mechano-targeted therapies that alter the mechanical environment of the joint could improve repair cartilage integration. Lubricin, a mucinous glycoprotein in the synovial fluid, has been well characterized as a cartilage boundary lubricant that effectively lowers interfacial shear strains.[3] Lubricin has been shown to have an anti-inflammatory role, but has not been evaluated in preclinical cartilage repair models. Recently, a bioengineering approach using codon scrambling was developed to produce a full-length recombinant human lubricin (rhLubricin).[4] While preliminary characterization has revealed that rhLubricin can lubricate cartilage, little is known about its ability to alter the quality of repaired cartilage. The goal of this study is to determine whether a single injection of rhLubricin can improve cartilage repair in an established New Zealand rabbit OCL defect model.[5] We hypothesize that lubricin injections will: (A) improve the quality of the total repair of the tissue, and (B) reduce the surface roughness of the repaired cartilage.

METHODS: *In vivo study design:* The NYU Institutional Animal Care and Use Committee approved all surgical procedures and experimental designs (IACUC 2017-0025). 4 mm diameter osteochondral (OCL) defects along with bone marrow stimulation (BMS) were performed on the medial femoral condyle of 18 New Zealand rabbits. rhLubricin and saline injections were performed 4-weeks after surgery. Control limbs received no defect or injection. Animals were euthanized at 12 weeks and the femoral condyles were collected (Fig 1). Two rabbits had surgical complications and were excluded from the analysis (rhLubricin: n = 9 joints; saline: n = 15 joints; unoperated control: n = 8 joints). *Surface Profilometry:* The root mean square surface roughness (R_q) was measured in the central region of the defect site on the medial femoral condyle using a Keyence VK-X260 optical profilometer. *Macroscopic evaluation of repair tissue:* To assess the quality of the repair, modified ICRS scores and Goebel scores were collected from 4-5 observers for the saline and rhLubricin group on the OCL repair site.[6] *Statistical analyses:* Statistical differences in surface roughness and repair tissue quality scores were calculated using a one-way ANOVA and a Wilcoxon rank sum test respectively.

RESULTS: Repair tissue from the rhLubricin treated group (Rq = 8.1 ± 2.7 μm) trended towards lower surface roughness compared to the saline treated group (Rq = 11.5 ± 5.6 μm, p = 0.056, Fig 2). Gross condyle scorings of total modified ICRS scores were graded on a scale from 0 (fully degenerated) to 16 (intact native cartilage) and indicated that samples from the rhLubricin treated group had higher median repair scores relative to the saline group, however this difference was not significant (rhLubricin = 10 ± 2, saline = 8 ± 2; p = 0.11, Fig 3A). Similarly, total Goebel scores were graded on a scale from 0 (fully degenerated) to 20 (intact native cartilage). While the total score for the rhLubricin treated group was higher than the saline group, this difference was not significant (rhLubricin = 14 ± 2, saline = 11 ± 2; p = 0.26, Fig 3B).

DISCUSSION: In this study, we show that rhLubricin injections 4 weeks after surgery decreased surface roughness of the repair tissues. Lubricin supplementation has been shown to inhibit integrative repair of cartilage due to its anti-adhesive properties,[7] but lubricin is critical for proper joint lubrication, maintaining low friction, and preserving cell viability.[8] Previously, lubricin injections performed immediately after the creation of OCL defects inhibited poor integration between repair and native cartilage.[7] However, the timing of the injection was immediately after the creation of the defect. In contrast, our study suggests that allowing a moderate level of infill before injection can improve the surface roughness of the defect and as well as improve the quality of the repair tissue. Notably, the rhLubricin injected joints showed decreased surface roughness compared to saline injected joints, which is concomitant with improved lubricating ability of the cartilage.[9,10] While the gross condyle scores using the modified ICRS and Goebel scoring methods indicated better quality of repair for the rhLubricin group compared to the saline group, this difference was not statistically significant.

SIGNIFICANCE: This study is the first to quantify the quality of repair in a OCL defect in a preclinical model after a single injection of a recombinant lubricin. The rhLubricin treated limbs showed trends of reduced surface roughness and higher repair tissue quality scores, which may improve the lubricating ability and mechanical properties of the repair tissue.

REFERENCES: [1] Irwin+2020 [2] Bonnevie+2018 [3] Gleghorn+2009 [4] Shrurer+2019 [5] Yasui+2021 [6] Goebel+2012 [7] Schaefer+2004 [8] Waller+2013 [9] Middendorf+2020 [10] Bonnevie+2017

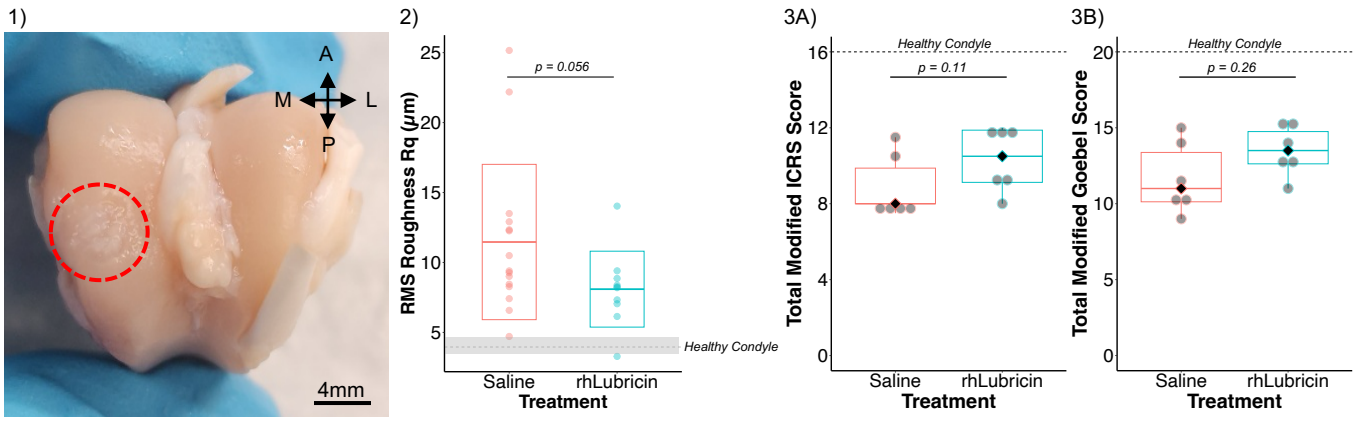

Figure 1) Right femoral condyle with medial OCL defect highlighted in red (A – anterior, P – posterior, M – medial, L – lateral). Figure 2) Surface roughness for saline and rhLubricin shows a trend of lower roughness in the rhLubricin group. Dashed line indicates average value for control condyles. Figure 3A) Modified ICRS scores and 3B) Goebel scores for cartilage repair for saline and rhLubricin. Dashed line indicates a score for a healthy condyle, diamond indicates median score.