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Mechanical motion induces *Prg4* expression in articular cartilage via CREB-dependent signaling pathways.

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Lubricin is a proteoglycan encoded by the *Prg4* locus, that is expressed by superficial zone articular chondrocytes and synoviocytes. Lubricin is thought to be critical to maintain boundary lubrication of diarthrodial joints. Although *Prg4* expression has been noted to be sensitive to mechanical loading, signaling pathway by which mechanical motion regulates *Prg4* expression is poorly understood. The purpose of this study is to elucidate this signaling pathway.

METHODS: To examine whether voluntary wheel running could affect the *Prg4* expression in knee articular cartilage, we have developed *Prg4*$^{GFPCreERt2/+}$*; Rosa26*$^{floxlacZ/+}$ mice. We housed these mice without/with access to a running wheel, and observed articular cartilage by X-Gal staining and immunostaining. Mouse chondrocytes were cultured on a rotary shaker to be applied with fluid flow shear stress (FFSS).

RESULTS: After 1 month of running, *Prg4*$^{GFPCreERt2/+}$*; Rosa26*$^{floxlacZ/+}$ mice displayed the double number of cells expressing □-gal. FFSS promoted the secretion of PGE2, ATP and PTHrP, and thereby their paracrine effect activated CREB via Gs-cAMP-PKA and Ca^{++}-CRTC1 pathways for *Prg4* expression. Because either FFSS in vitro or wheel running exhibited similar change of key molecules, it seems that wheel running induces the mechano-stimulated responses via similar signaling pathways.

DISCUSSION: In this study, we showed how cartilage/chondrocytes translates mechanical stimulation into biochemical signals. The understanding this signaling pathways potentially provides a new therapeutic opportunity employing small molecule or physical therapy, to modulate *Prg4* expression and thus stem cartilage degradation in osteoarthritis.