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Low-intensity pulsed ultrasound (LIPUS) treatment of cultured chondrocytes stimulates production of CCN family protein 2 (CCN2), a protein involved in the regeneration of articular cartilage: mechanism underlying this stimulation

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Abstract

Objective: CCN family protein 2/connective tissue growth factor (CCN2/CTGF) promotes cartilage regeneration in experimental osteoarthritis (OA) models. However, CCN2 production is very low in articular cartilage. The aim of this study was to investigate whether or not CCN2 was promoted by cultured chondrocytes treated with low-intensity pulsed ultrasound (LIPUS) and to clarify its mechanism.

Methods: Human chondrocytic cell line (HCS)-2/8, rat primary epiphyseal and articular cartilage cells, and Ccn2-deficient chondrocytes that impaired chondrocyte differentiation, were treated with LIPUS for 20 min at 3.0 MHz frequency and 60 mW/cm^2 power. Expressions of chondrocyte differentiation marker mRNAs were examined by real-time PCR (RT-PCR) analysis from HCS-2/8 cells and Ccn2-deficient chondrocytes at 30 min and 1 h after LIPUS treatment, respectively. CCN2 production was examined by Western blotting after 5 h of LIPUS treatment. Moreover, Ca^{2+} influx was measured by using a Fluo-4 probe.

Results: The gene expression of chondrocyte differentiation markers and CCN2 production were increased in cultured chondrocytes treated with LIPUS. In addition, Ca^{2+} influx and phosphorylation of p38 mitogen-activated protein kinase (MAPK) and extracellular signal-regulated kinase (ERK)1/2 were increased by LIPUS treatment, and the stability of TRPV4 and BK_{ca} channel mRNAs was decreased by siRNA against CCN2. Consistent with those findings, the LIPUS-induced the gene expressions of type II collagen (COL2a1) and Aggrecan (ACAN) observed in wild-type cells were not observed in the Ccn2-deficient chondrocytes.

Conclusion: These data indicate that chondrocyte differentiation represented by CCN2 production was mediated via MAPK pathways activated by LIPUS-stimulated Ca^{2+} influx, which in turn was supported by the induced CCN2 molecules in articular chondrocytes.

Keywords: Actin polymerization; CCN family 2/connective tissue growth factor (CCN2/CTGF); Calcium ion channels; Chondrocytes; Low-intensity pulsed ultrasound (LIPUS).

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