Deficiency of Cartilage-Specific Y-box Binding Protein 1 Represses NF-κB Signaling and Alleviates Osteoarthritis Progression

Zhao Zhang, Yucan Ju, Zeyu Huang*

Department of Orthopaedic Surgery, Orthopaedic Research Institute, West China Hospital, West China Medical School, Sichuan University, Chengdu, China

Email address:

zhangzhaozz@stu.scu.edu.cn (Zhao Zhang), juyucan@163.com (Yucan Ju), zey.huang@gmail.com (Zeyu Huang)

*Corresponding author

Abstract

Objective: This study aimed to elucidate the role of Y-box binding protein 1 (YBX1) in the pathogenesis of osteoarthritis (OA), with a focus on its molecular mechanisms and therapeutic potential. *Methods*: Proteomic and phosphoproteomic analyses were conducted to compare intact and osteoarthritic regions of cartilage obtained from patients undergoing total knee arthroplasty, revealing a significant upregulation of YBX1 in diseased tissue. To investigate its functional role, medial meniscus destabilization surgery was performed on both normal C57BL/6 mice and cartilage-specific YBX1-deficient mice, followed by comprehensive behavioral, micro-computed tomography, and histological assessments. YBX1 was overexpressed in the C28/I2 chondrocyte cell line, and potential binding partners were identified through immunoprecipitation coupled with mass spectrometry. Additionally, MedChemExpress drug libraries were screened for small-molecule inhibitors of YBX1, and promising candidates were administered intra-articularly in a mouse OA model to evaluate their therapeutic efficacy. *Results*: Total YBX1 and its phosphorylation at S102 were significantly elevated in osteoarthritic compared to intact human cartilage. Genetic ablation of YBX1 in chondrocytes markedly attenuated disease progression in the OA mouse model. Overexpression of YBX1 in chondrocytes activated NF-κB signaling, a key pathway in OA pathogenesis. Phosphorylation of YBX1 at S102 disrupted its interaction with TRIM56, facilitating its nuclear translocation. Within the nucleus, YBX1 inhibited NF-κB-repressing factor (NKRF), leading to the upregulation of NF-κB target genes. Virtual drug screening identified hesperidin methylchalcone and mulberroside A as potent inhibitors of YBX1 phosphorylation at S102. Intra-articular administration of either compound effectively alleviated OA progression in the injury-induced mouse model. *Conclusion*: YBX1 contributes to OA progression by inhibiting NKRF and subsequently activating NF-κB signaling. Phosphorylation of YBX1 at S102 plays a critical role in this process, making it a potential therapeutic target. Our findings suggest that targeting YBX1, particularly through inhibition of its phosphorylation, represents a promising strategy for the treatment of OA. This study provides novel insights into the molecular mechanisms underlying OA and highlights the therapeutic potential of YBX1 modulation.

Keywords

YBX1, NF-κB Signaling, Osteoarthritis, Chondrocytes, NKRF, Phosphorylation