Casein kinase II subunit β contributes to the progression of osteoarthritis via NF-κB pathway in inflammatory environment

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INTRODUCTION: Osteoarthritis (OA) is the most prevalent joint disease worldwide, causing chronic disability in elderly population. In OA, the synovium and chondrocytes release inflammatory cytokines, chemokines, and other agents of inflammation. In this reason, inflammatory pathway plays a crucial role in the OA progression. Many studies have shown that the family of nuclear factor-kappaB (NF-κB) signaling pathways, which regulates the expression of numerous genes associated with the inflammatory response, contribute to the pathogenesis of OA. Recently, it also has been revealed that CK2 is involved in various signaling pathway such as PI3K/Akt pathway, JAK2/STAT3 pathway including NF-kB pathway. Although there are many reports that CK2 promotes NF-kB at a post-translational level, its role in OA is still unclear. In the present study, we clarified the regulatory mechanism of CK2β -IκB-NF-κB axis in OA.

METHODS: Human cartilage samples were obtained from 5 patients undergoing total knee arthroplasty with OA, with approval from the Institutional Review Board (IRB) (2019-1374-002) of the Yonsei University College of Medicine. Human cartilage tissues were divided into two groups: the site of intact tissues or the site of damaged tissues. An in vitro model to mimic the OA environment was established with TNF-α in TC28a2 normal human chondrocyte cell line. To check the protein and mRNA levels of CK2β, we performed immunohistochemistry (IHC) and real-time PCR. Immunoprecipitation (IP) was performed to reveal interaction between CK2β and IkBα. We used a conditional knockout (cKO) mice with cartilage-specific deletion of the Csnk2b gene for DMM surgery experiments.

RESULTS SECTION: In this study, we found that CK2 activity and the expression of CK2β were elevated in human knee cartilage tissue affected by osteoarthritis. Also, the inhibition of CK2β expression was alleviated TNF-α-induced inflammatory reactions in TC28a2. Additionally, we confirmed that CK2β contributes to the NF-κB-mediated inflammatory response by directly phosphorylating NF-κB p65 and IκB in chondrocytes. Furthermore, we confirmed the activation of IκB- mediated NF-κB signaling in human OA cartilage tissues. In *in vivo*, Csnk2b cKO mice showed a protective effect on the OA-like phenotypes.

DISCUSSION: We discovered a correlation between elevated CK2β levels in human osteoarthritis (OA) and the progression of OA. Moreover, we elucidated the functions of CK2β as a regulator of the NF-kB mediated inflammatory reaction within chondrocytes. In this study, the CK2β have a pivotal role in the progression of OA via CK2β -IκB-NF-κB pathway. This study is the first to show the regulation of the CK2β contribute to maintain chondrocyte homeostasis under inflammatory conditions of OA.

SIGNIFICANCE/CLINICAL RELEVANCE: Our findings reveal that upregulation of CK2β in human OA is related to the OA progression, suggesting that the regulation of CK2β -IκB-NF-κB axis in chondrocytes could prevents osteoarthritic inflammatory response.

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IMAGES AND TABLETS: