Zfp521 delays osteoarthritis by inhibiting chondrocyte hypertrophy and senescence via intranuclear HDAC4

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INTRODUCTION: Osteoarthritis (OA) is a total joint disease characterized by disturbances in cartilage homeostasis leading to subsequent inflammation and degeneration resulting in chronic pain and functional impairment. The pathologic and molecular mechanisms underlying the onset and progression of this disease are unknown, and therefore there are currently no effective disease-modifying treatments available. Zfp521 effectively inhibits hypertrophic differentiation of growth plate cartilage in the physiological state, but its role in the inflammatory environment of OA remains unclear.Therefore, we explored the effect of Zfp521 on the course of OA by modulating its expression in chondrocytes and rat models.

METHODS: Zfp521 was overexpressed or silenced in chondrocytes to test its effects on proliferation, apoptosis, and ECM homeostasis. Zfp521 overexpressing adenovirus was injected into the knee joint cavity of ACL transection rats to detect its delaying effect on osteoarthritis. And the molecular mechanism of Zfp521 in cartilage degeneration was explored in combination with proteomics analysis.

RESULTS SECTION:Zfp521 can effectively promote chondrocyte proliferation. And by inhibiting chondrocyte hypertrophy, thus maintaining cell phenotype and reducing apoptosis. In addition, EdU assay and FMT assay showed that Zfp521 could promote chondrocytes to enter the cell cycle and reduce the secretion of senescence-related proteins, and ultimately maintain the balance of anabolism and catabolism in ECM.The above functions of Zfp521 acted through the nucleus of the cell via the histone deacetylase 4 (HDAC4), and the function of Zfp521 was significantly weakened when there was no HDAC4 in the nucleus In the absence of HDAC4 in the nucleus, Zfp521 function is significantly reduced.

DISCUSSION: Zfp521 reduces chondrocyte apoptosis by inhibiting cellular hypertrophy and senescence phenotype. It also exerts therapeutic effects on OA by maintaining the metabolic homeostasis of articular cartilage through its pro-proliferative effects.The physiological effects of Zfp521 are dependent on the content of HDAC4 in the nucleus of the cell, and increasing the intranuclear content of HDAC4 is a promising strategy for the treatment of OA.The limitation was that since Zfp521's attenuation of OA is dependent on HDAC4 in the nucleus, further investigation is required to deter mine whether increasing both HDAC4 and Zfp521 levels in chondrocytes will yield better therapeutic effects.

SIGNIFICANCE/CLINICAL RELEVANCE: The pathology and molecular mechanisms of OA are unknown, and with the progressive aging of the general population, there is an urgent need for effective drugs to treat OA . The effectiveness of Zfp521 in preclinical studies makes it a potential drug target.

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