IGFBP7 secreted from senescent chondrocyte exacerbates osteoarthritis progression via inducing paracrine senescence

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INTRODUCTION: Accumulation of senescent chondrocytes contributes to osteoarthritis (OA) progression by altering the joint microenvironment. The secretion of senescence-associated secretory phenotypes (SASPs) from these senescent chondrocytes is thought to induce paracrine senescence in neighboring normal chondrocytes. However, the underlying pathogenic mechanisms in OA progression are not fully understood. Here, we identify insulin-like growth factor-binding protein 7(IGFBP7) as a potential paracrine senescence factor and investigated its role in OA progression.

METHODS: To confirm its paracrine senescence, we collected conditioned media (CM) from senescent chondrocytes and treated them to normal chondrocytes. Then, we conducted senescence-associated β-galactosidase (SA-β-Gal), proliferation, mRNA expression of p16 and p21 to measure the senescence phenotype. To identify potential paracrine factors, we analyzed the Gene Expression Omnibus (GEO) database and OA patient-derived chondrocytes and conducted western blot and enzyme-linked immunosorbent assay (ELISA) in synovial fluid and OA cartilage. Then we treated recombinant IGFBP7 to normal chondrocytes and confirmed its role in senescence induction. By treating IGFBP7 neutralizing antibody, we evaluated inhibition of senescence induction by IGFBP7. To validate in vivo, we conducted intra-articular injection of IGFBP7 protein and the neutralizing antibody in a rat OA model.

RESULTS SECTION: When treated with CM, SA-β-gal activity and p16, p21 expression were increased, while proliferation was decreased. The results of analyzed GEO database and OA patient's chondrocytes showed IGFBP7 mRNA expression are elevated in OA chondrocytes. In addition, IGFBP7 protein levels were upregulated in synovial fluid and OA cartilage. Additionally, IGFBP7 treatment led to an increase in the mRNA expression of anabolic markers (SOX9, CO2A1, and ACAN) and a decrease in catabolic markers (MMPs and ADAMTS5). In contrast, blocking IGFBP7 using a neutralizing antibody significantly attenuates chondrocyte senescence. Intra-articular injection of IGFBP7 in a rat OA model exacerbated OA progression and accumulation of senescence chondrocyte. Conversely, IGFBP7 antibody injection showed cartilage protective effects, confirmed by intact cartilage, increased collagen type 2 and decreased MMP13 expression.

DISCUSSION: These findings demonstrate that IGFBP7 plays a significant role in OA progression by inducing paracrine senescence in surrounding normal chondrocytes and antibody-mediated targeting of IGFBP7 could be a promising therapeutic approach for OA.

SIGNIFICANCE/CLINICAL RELEVANCE: This study identified the paracrine senescence of IGFBP7 in OA and confirmed that its neutralizing antibodies can inhibit the progression of OA.

IMAGES AND TABLES:

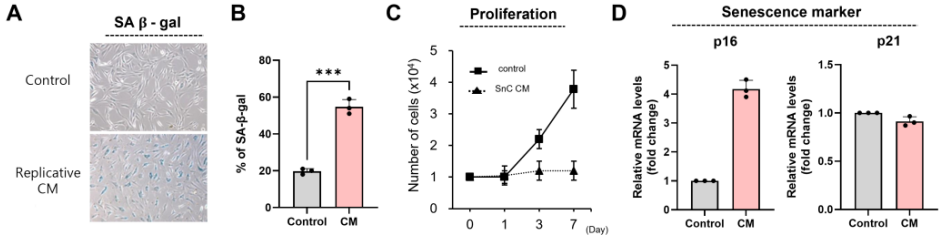

Figure 1. Treatment of conditioned media from senescence chondrocytes induced paracrine senescence.

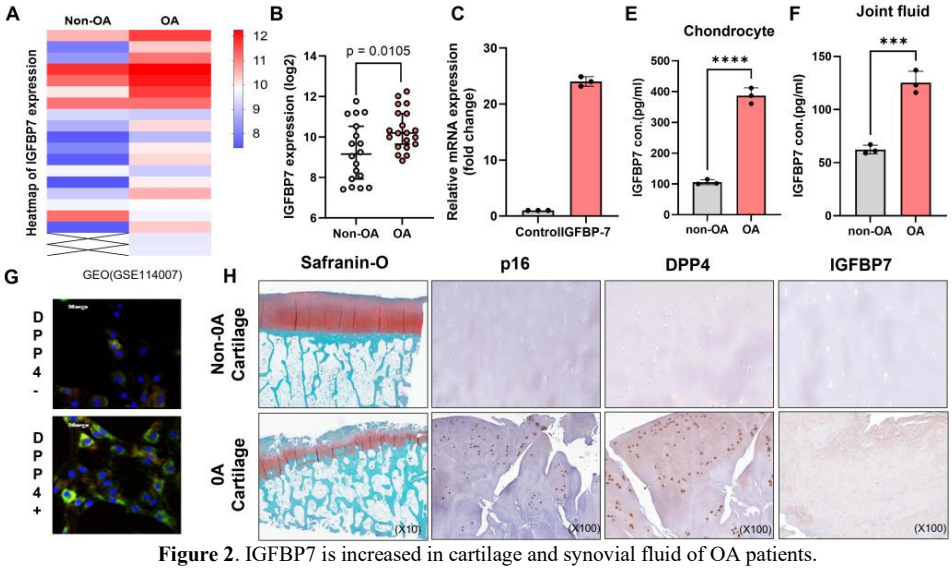

Figure 2. IGFBP7 is increased in cartilage and synovial fluid of OA patients.