KLF15 deficiency exacerbates osteoarthritis through reduced expression of PPARγ signaling in mice

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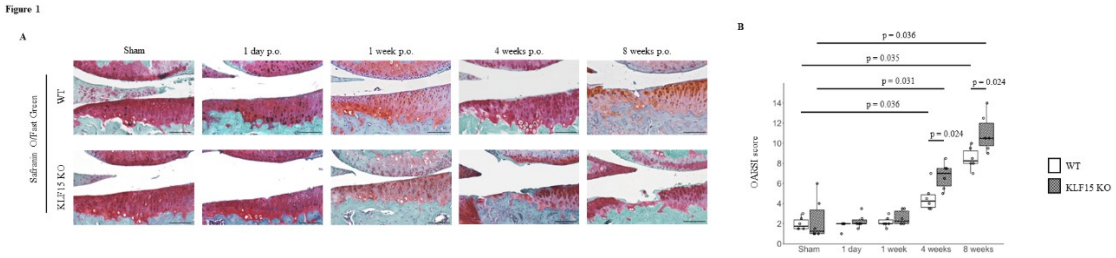
INTRODUCTION: Krüppel-like factor 15 (KLF15) expression is significantly lower in the chondrocytes of patients with OA than in those from normal participants, and KLF15 reduces the expression of MMP3 at the transcriptional level (2). KLF15 plays an essential role in adipogenesis by regulating PPARγ expression through its binding to different sites in the promoter of PPARγ2, enhancing its promoter activity (3). This study aimed to evaluate the association between deficient KLF15 expression and OA progression in an experimental mouse model.

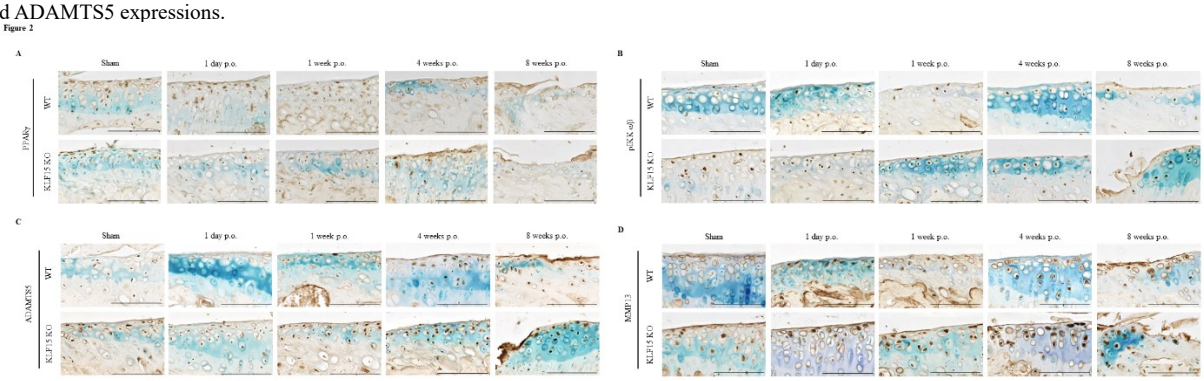
METHODS: Tamoxifen-induced cartilage-specific KLF15 knockout (KO) mice were generated. 10-week-old male wild-type (WT) mice and KLF15 KO mice was performed destabilization of the medial meniscus (DMM) surgery to induce OA. Immunohistochemistry were performed. In the *in vitro* setting, immunofluorescence, RT-PCR, and western blot analyses were performed.

RESULTS:

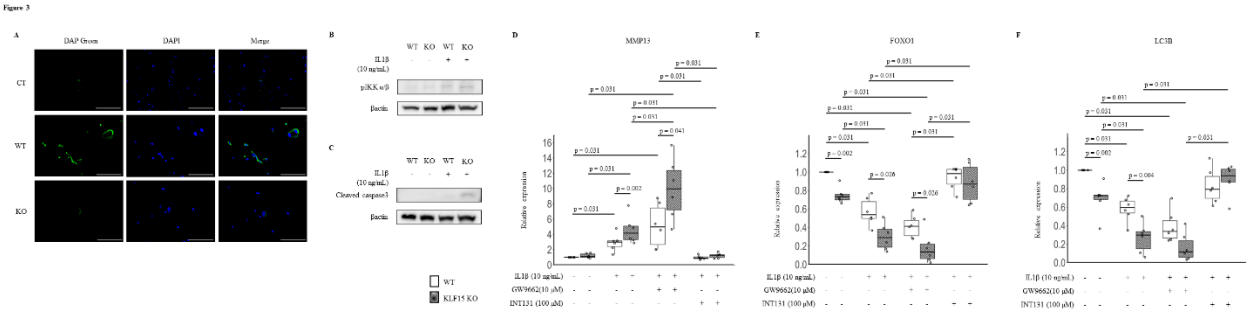
1. KLF15 KO DMM mice exhibited significant cartilage degradation compared to WT mice. According to the OARSI cartilage OA histopathology scoring system, the mean sum score of the KLF15 KO mice was significantly higher than that of the WT mice at 4 and 8 weeks after surgery ($P = 0.024$ and $P = 0.024$, respectively).



2. Immunohistochemistry results revealed KLF15 KO mice susceptibility to OA changes with reduced PPARγ expression and enhanced pIKKα/β, MMP13, and ADAMTS5 expressions.



3. The RT-PCR and western blotting confirmed in vivo results that KLF15 deficiency increased pIKKα/β and MMP13 expressions and inhibited autophagy with reduced FOXO1 and LC3B expression. PPARγ agonist (INT131) cancelled IL1β-induced catabolic effects.



DISCUSSION:

KLF15 deficiency is susceptible to OA changes accompanied by reduced autophagy, and increased apoptosis. We showed that the OA phenotype of KLF15 KO DMM mice was influenced by reduced PPARγ expression, including enhanced pIKKα/β, ADAMTS5, and MMP13 expression through IKKα/β, reduced autophagy, and increased apoptosis.

SIGNIFICANCE/CLINICAL RELEVANCE: The results suggested that testing KLF15 as an osteoarthritis therapeutic should be a focus in further research.

REFERENCES:

1. Fahmi H, Martel-Pelletier J, Pelletier JP, Kapoor M. Peroxisome proliferator-activated receptor gamma in osteoarthritis. Mod Rheumatol 2011;21:1-9.
2. Li Y, Zhao M, Xiao W. KLF15 Regulates the Expression of MMP-3 in Human Chondrocytes. J Interferon Cytokine Res 2018;38:356-362.
3. Gray S, Feinberg MW, Hull S, Kuo CT, Watanabe M, Sen-Banerjee S, et al. The Kruppel-like factor KLF15 regulates the insulin-sensitive glucose transporter GLUT4. J Biol Chem 2002;277:34322-34328.