KLF15 affects the progression of arthropathy in inflammatory arthritis

Kensuke Anjiki, Shinya Hayashi, Kenmei Ikuta, Yuma Onoi, Shotaro Tachibana,Yoshihito Suda, Kensuke Wada, Akira Saito, Takuma Maeda, Tomoyuki Kamenaga, Masanori Tsubosaka,Yuichi Kuroda, Naoki Nakano,Tomoyuki Matsumoto,Ryosuke Kuroda

Department of Orthopaedic Surgery, Kobe University School of Medicine, Kobe, Japan

Disclosures: All authors (N)

INTRODUCTION: Kruppel-like zinc finger transcription factor 15 (KLF 15) is a transcription factor that regulates physiological systems[1]. It is also reported that KLF15 regulates adipocyte differentiation via PPARγ, and PPARγ suppresses joint inflammation via the NFk-B pathway[2,3]. The purpose of this study was to clarify the effects of KLF15 in a mouse Collagen Antibody Induced Arthritis (CAIA) model.

METHODS: Tamoxifen-induced cartilage-specific KLF15 knockout (KO) mice were generated and tamoxifen was administered intraperitoneally for 5 consecutive days at 6 weeks of age. An anti-type II collagen monoclonal antibody was intraperitoneally administered to 10-week-old male KO mice (KO group) and wild-type mice (WT group). On the 3rd day after administration, Lipopolysaccharaide（LPS）was additionally administered to create a mouse CAIA model. In both groups, the knee joints were collected at 0, 1, 2, and 4 weeks after antibody administration, and were evaluated histologically (safranin-O, HE), immunohistologically (PPARγ, pIKK α/β, IL-1β, MMP3, MMP-13) were evaluated and compared between the two groups.

RESULTS: The arthropathy score was significantly higher in the KO group at 4 weeks, and the synovitis score did not differ significantly at each time point (Figure.1). At each time point, PPARγ decreased significantly in the KO group (Figure.2), and pIKK α/β, IL-1β, MMP-3, and MMP-13 increased significantly in the KO group (Figure.3).

DISCUSSION: Induction of arthritis in cartilage-specific KLF15KO mice increased inflammatory markers and matrix-degrading enzymes in cartilage and suppressed cartilage degeneration. Decreased anti-inflammatory PPAR-γ expression in articular cartilage increased its downstream pIKK α/β. As a result, it was possible that IL-1β, MMP-3, 13 expression was significantly increased locally in the articular cartilage.

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

REFERENCES: **1**. Hirata et al. JCI Insight. 2019. **2**. Mori et al. J Biol Chem. 2005. **3**. Shiojiri T. Eur J Pharmacol. 2002.

Figures:

Figure.1

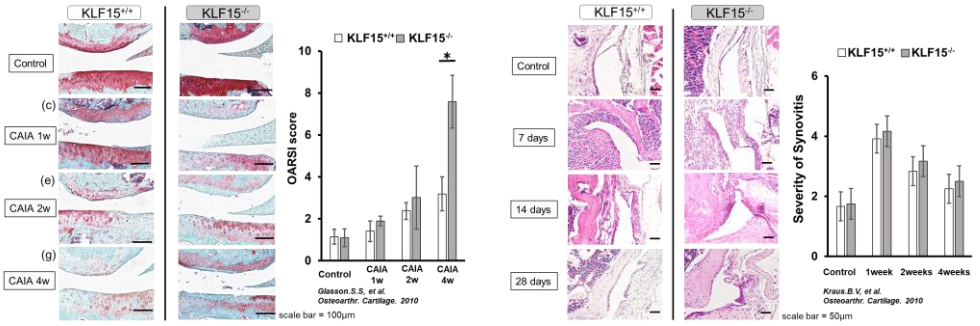

Figure.2

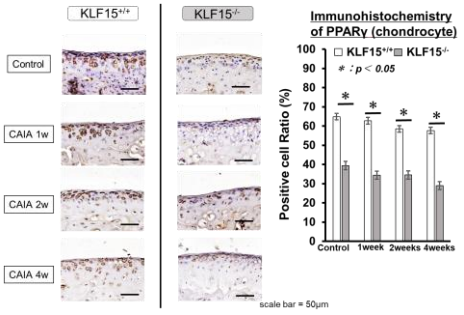

Figure.3