Abstracts

TRANSGLUTAMINASE-2 IN OSTEOARTHRITIS: MMP-13 PRODUCTION THROUGH ENHANCED FOXO3A NUCLEAR TRANSLLOCATION

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Introduction Transglutaminase 2 (TG2) also known as tissue transglutaminase, is a calcium-dependent enzyme that has a variety of intracellular and extracellular substrates. It has been well known that TG2 increases in osteoarthritis (OA) tissue and can be used as a biomarker of OA.

Objectives To elucidated the molecular mechanism of TG2 during the cartilage degradation in OA.

Methods The surgical destabilisation of the medial meniscus (DMM) model is used to induce OA in 10-week-old male C57BL/6J mice. Primary chondrocytes were obtained from E15.5 long bones, and ZDON, a cell-permeable, peptide-based, irreversible inhibitor of TG2, was used to inhibit the function of TG2 and calcium ionophore to stimulate TG2.

Results TG2 expression was increased in articular cartilage and growth plate in surgical OA model. When treated with various growth factors, only TGFβ1 increased TG2 expression of primary chondrocyte in a dose-dependent manner. Intra-articular injection of specific TG2 inhibitor, ZDON, ameliorated the severity and MMP-13 expression in surgically-induced OA. ZDON attenuated MMP-3 and MMP-13 expression in TGFβ1- and calcium ionophore-treated chondrocytes in a Runx2-independent manner. TG2 activation by calcium ionophore induced phosphorylation of FoxO3a and ZDON decreased total FoxO3a as well as nuclear FoxO3a level. FoxO3a and TG2 were co-localised in primary chondrocytes and immunoprecipitation analysis revealed a direct interaction of FoxO3a and TG2, suggesting enhanced nuclear translocation of FoxO3a by TG2.

Conclusions Our data provide an evidence of TG2 as an enhancer of FoxO3a-nuclear translocation which was responsible for the TG2-dependent MMP-13 expression.

Disclosure of interest None declared

REFERENCES


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