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Reduced expression of MMP-10 through FGF8/FGFR3 signal pathway in Kashin-Beck disease and its potential role in differentiation apoptosis of chondrocytes

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Kashin-Beck disease (KBD) is a chronic, deforming endemic osteoarticular disease. Chondrocyte death and abnormal differentiation in the hypertrophic layer of the growth plates is a known feature of KBD. MMP-10 is one of members of the matrix metalloproteinase family and involved in the degradation of extracellular matrix in the normal physiological processes. Therefore, we hypothesized that MMP-10 deficiencies is largely responsible for abnormal terminal differentiation and chondrocyte death and may play an important role in cartilage death and KBD. MMP-10 in the cartilages of KBD were visualized by immuno histochemistry, their protein levels were determined by western blotting in cartilage of KBD patients and in the T-2 toxin and selenium (Se) deficiency induced rat model. ATDC5 cells were cultured for 21 days in insulin transferrin sodium selenite and the model of hypertrophic chondrocytes was constructed in vitro. MMP-10 deficiencies on chondrogenic ATDC5 cells through shRNA mediated gene silencing of MMP-10. Specific inhibitor BGJ398 for FGFR3 was used to block the FGF8/FGFR3 signal pathway. The expression of chondrocyte differentiation related genes was detected by real time PCR and western blot. Hypertrophic chondrocyte death of knock down MMP-10 was detected using flow cytometry. Results showed that MMP-10 positive red staining was found in the whole layer of the epiphyseal plate but mainly in hypertrophic layer in the normal group. While the expression of MMP-10 was decreased in KBD children epiphyseal plate and in rats fed with normal or Se deficiency diets plus T-2 toxin. Meanwhile, MMP-10 proteins and mRNA levels was increased in ATDC5 cells induced by ITS at 7d, 14d and 21d compared with 0d. Specific inhibitor BGJ398 for FGFR3 could partly block the T-2 toxin induced down regulation of MMP-10 level. MMP-10 deficiency in chondrocytes in different differentiation stages resulted in decreased expression of type II collagen and hypertrophic chondrocyte markers Runx2, type X collagen and MMP-13. MMP-10 deficiencies could promote the apoptosis of chondrocytes, including early chondrocyte apoptosis. MMP-10 is indispensable for chondrogenic differentiation; especially osteogenesis through FGF8/FGFR3 signal pathway, suggesting that down regulation of MMP-10 in KBD may lead to chondrocyte terminal differentiation disorder and excessive apoptosis of chondrocytes by impacting cartilage extracellular matrix remodeling. Therefore, MMP-10 deficiency impaired differentiation and death of chondrocytes through FGF8/FGFR3 signal pathway may be the pathological mechanism of the osteoarthropathy of KBD.

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