LOSS OF NPP1 INDUCES CARTILAGE REMODELLING INTO BONE AND OA-LIKE CHANGES IN MICE

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Background Cartilage calcification is common in osteoarthritis (OA) and correlates with the severity of cartilage breakdown. Nucleotide pyrophosphatase phosphodiesterase 1 (NPP1) contributes to maintain an optimal balance of pyrophosphate (PPi) and phosphate (Pi) in the extracellular matrix, thereby, together with the phosphate regulating molecules progressive ankylosis protein (ANK) and tissue nonspecific alkaline phosphatase (TNAP), preventing the generation of calcium crystals. Previous data have demonstrated regulation of NPP1 expression by inflammatory mediators and linked it to pathological cartilage calcification.

Methods Cartilage explants were obtained from 120 consecutive patients with OA undergoing joint replacement. Experimental OA was induced in mice by resection of the anterior cruciate ligament. Cartilage calcification was evaluated in human explants by digital contact radiography and in mice by fluorid positron emission tomography (PET)-scanning and μCT. The expression of NPP1, ANK and TNAP was performed by quantitative real time RT-PCR in human cartilage samples and by immunohistochemistry in experimental murine OA. Von Kossa-safranin-O staining was used to measure cartilage and meniscal calcification in mice carrying a homozygous loss of function mutation of ennpp1. The severity of OA was quantified using the Mankin Score. Cartilage remodelling was investigated using immunohistological stainings for collagen type I, collagen type X, osteopontin and TRAP.

Results In OA patients, the expression of NPP1, but not ANK and TNAP, inversely correlated with cartilage calcification (p<0.05). Such inverse correlation was confirmed in vivo in experimental murine OA. Using Fluoride PET, the authors showed enhanced calcification activity in joints as well as in cartilage of non-weight bearing areas, including ear cartilage, in NPP1−/− mice, thereby suggesting that mechanical stress is not required for induction of calcification. NPP1−/− mice developed typical OA changes as evaluated by histological analysis and in vivo imaging. Intriguingly, calcification processes were associated with increased expression of the hypertrophic marker collagen X and the bone marker collagen I. Finally, the authors detected osteoclasts at the interface between bone and cartilage.

Conclusion NPP1 is an important player in OA-associated cartilage calcification. Pathologic calcification in the NPP1−/− mice leads to cartilage remodelling into bone, thereby resembling aspects of hypertrophic maturation. Taken together, the data suggest that OA is characterised by the reactivation of molecular signalling cascades associated with endochondral ossification.