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EFFECT OF PPI STIMULATION ON OSTEOARTHRITIC ARTICULAR HUMAN CHONDROCYTES

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Purpose :

Osteoarthritis (OA) is the most common form of chronic joint disease, characterized by cartilage degeneration that results from complex changes in the chondrocyte phenotype. The presence of phosphate-containing microcrystals in the injured cartilage areas suggests the contribution of the phosphocalcic metabolism in the phenotype switch of some chondrocytes during the disease. The balance between the concentrations of inorganic pyrophosphate (PPi) and inorganic phosphate (Pi) present in the joint environment has emerged as an important regulator of the chondrocyte phenotype. If numerous studies have shown that elevated concentrations of extracellular Pi (ePi) or ePPi have, respectively, activating or repressive mineralizing effects on articular cartilage, we recently demonstrated that ePPi also prevents the *in vitro* dedifferentiation of articular chondrocyte in rats, an effect mostly triggered by Ank-induced release of PPi. This suggests that PPi may be an attractive candidate to prevent the phenotype switch of the articular chondrocyte observed in OA.

To confirm and validate our observation *in vitro*, we analyze the role of PPi in human chondrocyte phenotype alterations during osteoarthritis.

Methods :

We first determined PPi targets by proteomics, PCR arrays and ELISA analyzes in cartilage samples obtained from OA individuals, and then studied the consequences of *in vitro* extracellular PPi exposure on chondrocyte phenotype biomarkers and signaling pathways.

Gene expression studies were performed on OA human cartilage samples. Phenotypic biomarkers were studied by quantitative RT-PCR in human OA chondrocytes stimulated with 0.1mM of PPi. Protein activities were measured by ELISA. MAPK signaling was investigated by immunoblotting and the use of selective inhibitors.

Results :

Proteomics and PCR arrays showed that human OA chondrocytes stimulated with 0.1mM of PPi, displayed a decreased expression of collagen components of the matrix and sustained expression of MMPs and integrins. We confirmed that MMPs were increased by ELISA. Proteomics data also showed that PPi increased markers of hypertrophy such as VEGF and MMP13, whose activity was also increased as demonstrated by ELISA experiments.

At the same time, proteomics and ELISA showed that the expression of IGFBP3, a protein recently involved in OA, was up-regulated by PPi. Interestingly, these results are accentuated in medium supplemented with 100ug/ml of insulin.

We demonstrated further that PPi stimulation mostly activates P38 pathway and to a lesser extent ERK pathway to regulate the expression of its target genes.

Conclusion :

Altogether, in contrast to previous data obtained in rats, the results obtained in this study demonstrate that PPi seems to promote matrix-remodeling and differentiation of OA chondrocytes towards an hypertrophic phenotype, with a potential role of the insulin pathway *via* IGFBP3.