Usefulness of Glycolytic System Inhibitors to Regulate Intracellular Metabolic Variability in Osteoarthritis

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INTRODUCTION: Osteoarthritis (OA) of the knee progresses with age, and there are currently no effective drugs to inhibit its progression. In previous in vitro studies, we have shown that anaerobic glycolysis is enhanced in chondrocytes under inflammatory conditions. The glycolytic inhibitor 2-deoxyglucose (2-DG) inhibited IL-1β-stimulated glycolysis. Furthermore, 2-DG suppressed the expression of MMP-13, a cartilage matrix degrading enzyme, and maintained safranin O staining, indicating that 2-DG has a chondroprotective effect. In this study, we comprehensively investigated the intracellular metabolic changes of 2-DG by metabolomic analysis in order to explore the mechanism of its effect. We also examined the chondroprotective effect of 2-DG intra-articular injection using DMM (destabilization of medial meniscus), a mouse model of OA.

METHODS:In vitro study: Isolated bovine cartilage was stimulated with IL-1β and 2-DG was added. After the chondrocytes were collected, metabolomic analysis using capillary electrophoresis time-of-flight mass spectrometry was performed.
In vivo study: 9-week-old C57BL/6 mice underwent DMM surgery to induce OA. At 15 weeks of age, knee joint sections were stained with safranin O and the staining of the medial tibial articular cartilage was evaluated using the OARSI (osteoarthritis research society international) score.

RESULTS SECTION: Metabolomic analysis showed that lactate, the end product of glycolysis, and its intermediate products were enhanced by IL-1β stimulation, while 2-DG inhibited them. The intermediates of the citric acid circuit were also increased by IL-1β, indicating hypermetabolism, and 2-DG inhibited them as well. The malate/aspartate ratio, an indicator of energy production in amino acid metabolism, was increased by IL-1β, and the glutamate/2-oxoglutarate ratio, which indicates amino acid degradation, was decreased, indicating increased energy production due to enhanced amino acid metabolism. The glucose 6-phosphate/ribose 5-phosphate ratio, an indicator of the pentose pathway, was also increased. 2-DG partially suppressed these metabolic changes.
In the OA mouse model, OARSI scores averaged 3.7 in the control group and 1.0 in the 2-DG group, indicating a statistically significant improvement.

DISCUSSION: Metabolomic analysis revealed multiple metabolic changes in chondrocytes under IL1β-stimulated inflammation other than glycolysis, indicating crosstalk between metabolisms. 2-DG, a glycolytic system inhibitor, regulated this complex metabolic change. 2-DG intra-articular injection showed an inhibitory effect on OA progression in OA model mice. In OA model mice, intra-articular injection of 2-DG showed an inhibitory effect on OA progression, indicating that regulation of intracellular metabolic changes may be a novel therapeutic agent for OA.

SIGNIFICANCE/CLINICAL RELEVANCE: The results suggest that 2-DG, an inhibitor of the glycolytic system, controls intracellular metabolic changes and inhibits OA progression.