Multi-Species Bioinformatics and Experimental Validation Reveal Cysteine Metabolism Dysregulation as a Driver of Ferroptosis in Osteoarthritis

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Disclosures: NA

INTRODUCTION: Osteoarthritis (OA) was traditionally viewed as a mechanically driven disorder. However, emerging evidence implicated metabolic dysregulation in its pathogenesis. This study investigated the novel interaction among cysteine metabolism, ferroptosis, and OA progression, while evaluating the therapeutic efficacy of L-cysteine supplementation.

METHODS: Integrated transcriptomic analyses of mouse (GSE112641), rat (GSE118559), and human (GSE114007) OA cartilage datasets identified conserved metabolic perturbations. Proteomic and metabolomic profiling of human OA cartilage (3 patients, male and female included) validated pathway-level dysregulation. Mechanistic validation employed IL-1β-stimulated chondrocytes under cysteine-depleted conditions, with parallel assessment of ferroptosis markers, including expression of GPX4, SLC7A11 and TFRC, glutathione metabolism, iron accumulation, and lipid peroxidation. Therapeutic potential was further tested in a surgery-induced OA mouse model receiving L-cysteine.

RESULTS SECTION: Cross-species analysis revealed cysteine/glutathione metabolism as the most consistently dysregulated pathway in OA. Multi-omics profiling demonstrated dysregulation of cysteine/glutathione metabolism and ferroptosis in OA. In vitro cysteine deprivation triggered ferroptosis hallmarks in primary chondrocytes, including viability reduction, malondialdehyde (MDA) increase, and glutathione depletion. L-cysteine supplementation reversed these effects, restoring viability and normalizing redox balance. Our in vivo study results further demonstrated that L-cysteine supplementation reduces cartilage degeneration severity by protecting against ferroptosis and lipid peroxidation.

DISCUSSION: This study establishes cysteine metabolism as a master regulator of ferroptosis in OA pathogenesis. The mechanistic chain from cysteine depletion to glutathione collapse, iron overload, and lipid peroxidation explains chondrocyte loss patterns observed clinically. L-cysteine supplementation emerges as a dual-action therapy, simultaneously addressing oxidative stress and ferroptosis. These findings reposition OA as a metabolically driven disorder and provide actionable therapeutic targets for clinical translation.

SIGNIFICANCE/CLINICAL RELEVANCE: This study suggested that targeting cysteine metabolism and ferroptosis offers novel therapeutic avenues for OA treatment. Ultimately, this research underscores the potential of metabolic interventions in slowing or preventing OA progression, with significant implications for clinical management.

Cysteine reduction in OA cartilage induce ferroptosis to promote OA progression