Ultrasound-responsive nanoplatform for targeted chondrocyte therapy in osteoarthritis: mechanisms and therapeutic efficacy

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Osteoarthritis (OA) is the most common form of arthritis and a leading cause of disability in the elderly, with prevalence rising due to aging and obesity. Chronic low-grade inflammation plays a pivotal role in OA progression. Juglone(Jug), a natural phenolic compound derived from walnut tree, exhibits anti-inflammatory and anti-adipogenic properties, yet its therapeutic potential in OA remains unexplored.

Here, we investigated the effects and mechanisms of an ultrasound-responsive Juglone-loaded PLGA CM@HA nanoplatform Jug-PLGA-CM@HA) in OA. IL-1β stimulated primary mouse chondrocytes and destabilization of the medial meniscus (DMM) OA mouse models were employed. Using qPCR, histological staining, immunohistochemistry, scanning electron microscopy, von Frey testing, DARTS, proteomics, CRISPR-Cas9 knockout, co-immunoprecipitation, and immunofluorescence co-localization, we systematically elucidated the molecular actions of Juglone. Both in vitro and in vivo, Juglone promoted cartilage anabolic gene expression, suppressed catabolic and fibrotic genes, and alleviated OA-associated pain. Mechanistically, Juglone directly targets PLOD1 in chondrocytes, modulating P21 and MAPK signaling pathways to enhance anabolic activity while inhibiting catabolism and senescence. PLOD1 knockout reversed these effects, decreasing anabolic genes and increasing catabolic and senescence gene expression. Ultrasound-responsive Jug-PLGA CM@HA further enhanced targeted delivery, promoting knee joint repair and pain relief in DMM and CIOA mice. These findings reveal a novel non-invasive therapeutic approach for OA, demonstrating that Jug-loaded PLGA-CM@HA promotes cartilage regeneration and regulates chondrocyte metabolism via the PLOD1/P21/ERK axis. This work provides a foundation for the translational application of ultrasound-responsive drug delivery in OA therapy.

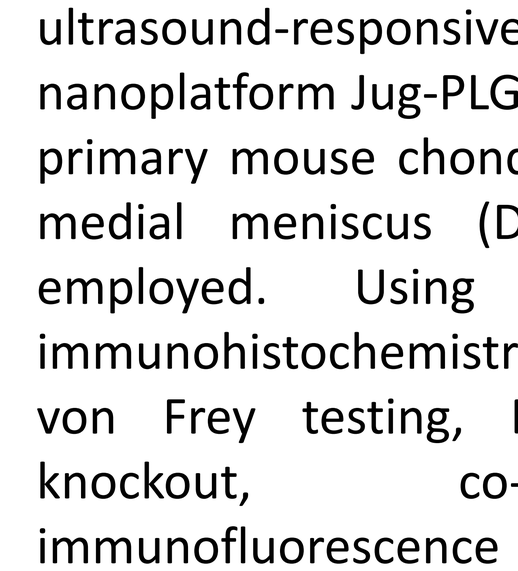


Fig.1 TEM images of the nanoparticles (up) and in vitro drug release profile of the drug-loaded nanoparticles (down). Scale bar = 100 nm.

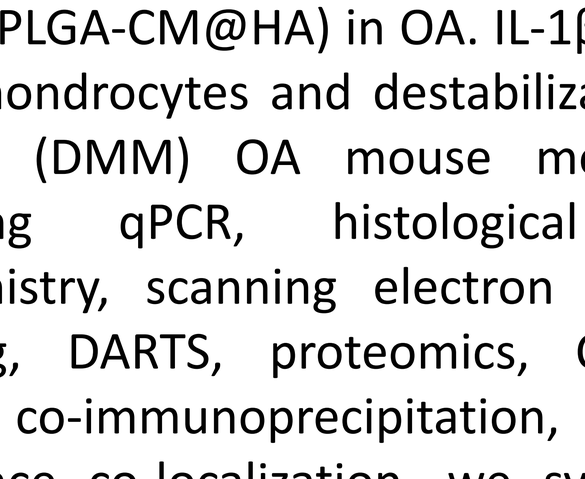


Fig.2 SEM images of HA hydrogel and Jug-PLGA-CM@HA hydrogel.

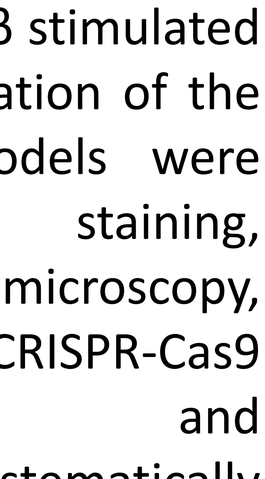


Fig.3 Fluorescence microscopy observation of the internalization of Jug-PLGA and Jug-PLGA-CM by C28/I2 chondrocytes.
Scale bar = 50 μm.

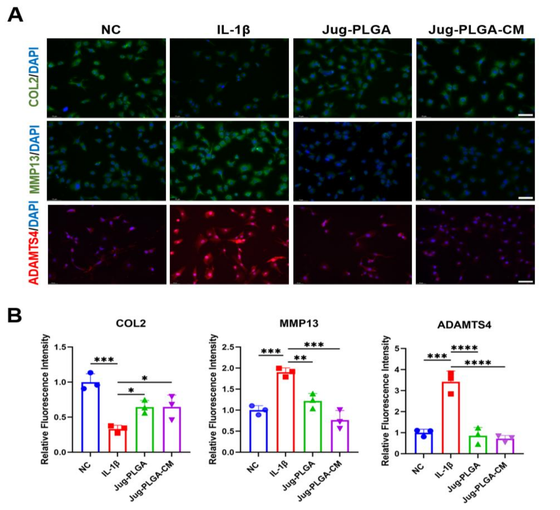


Fig.4 Immunofluorescence staining and quantitative analysis of gene expression in IL-1β-stimulated primary chondrocytes treated with Jug-PLGA or Jug-PLGA-CM. Scale bar = 75 μm.

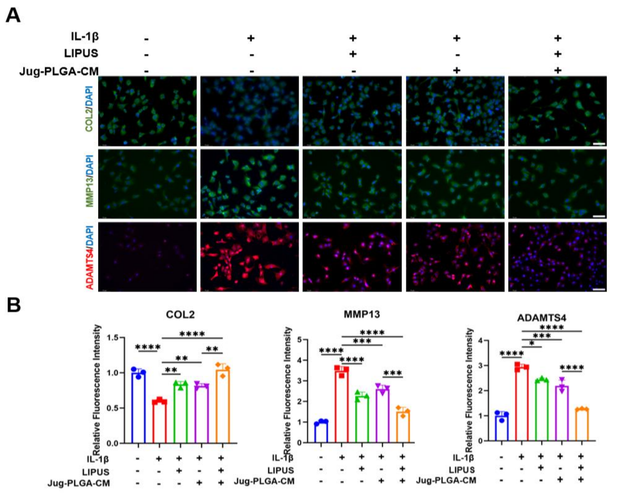


Fig.5 Immunofluorescence staining and quantitative analysis of gene expression in IL-1β-stimulated primary chondrocytes treated with LIPUS combined with Jug-PLGA-CM nanoparticles. Scale bar = 75 μm.

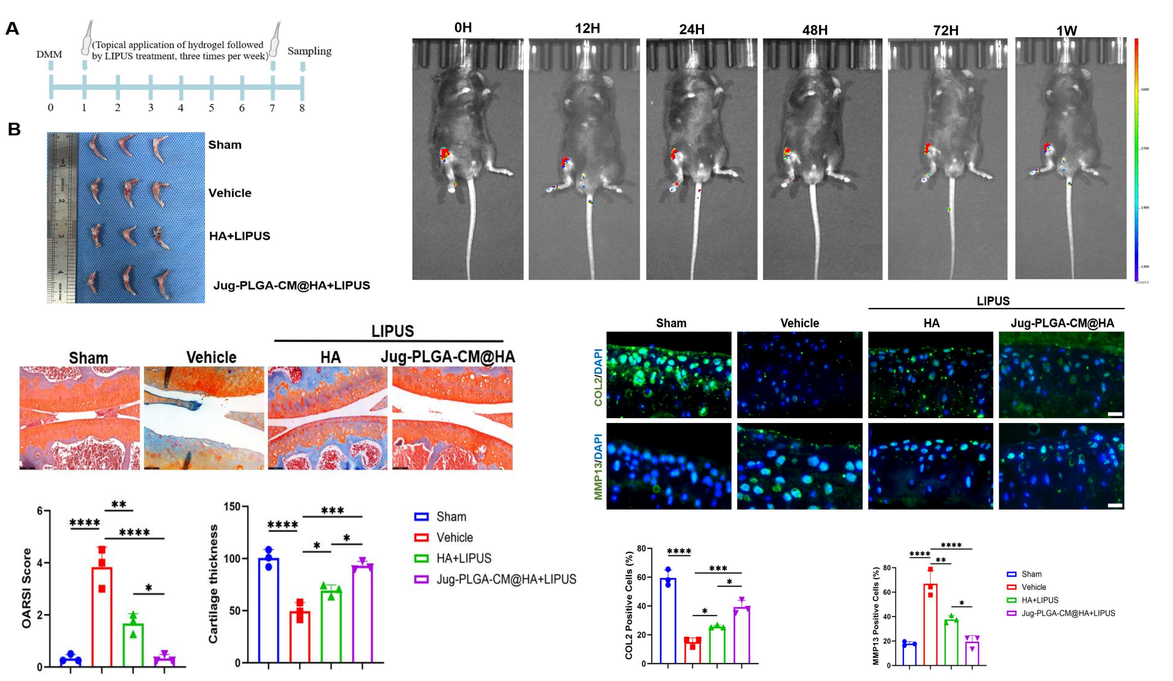


Fig.6 Therapeutic effects of LIPUS combined with intra-articular injection of Jug-PLGA-CM in DMM model mice.

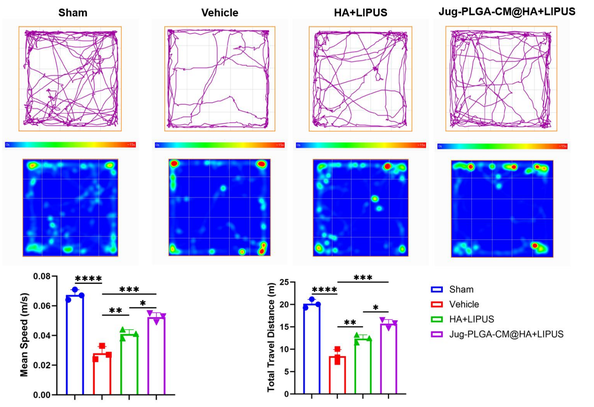


Fig.7 Open field test results with quantitative analysis of mean speed and total travel distance. Data are presented as mean ± SD (n = 3).

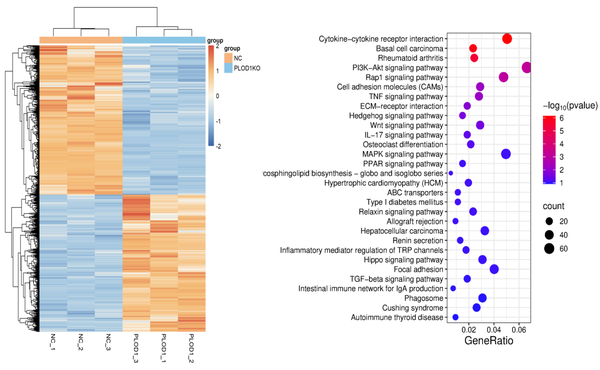


Fig.8 Heatmap of differentially expressed genes and bubble plot of KEGG pathway enrichment analysis between NC and PLOD1 KO groups

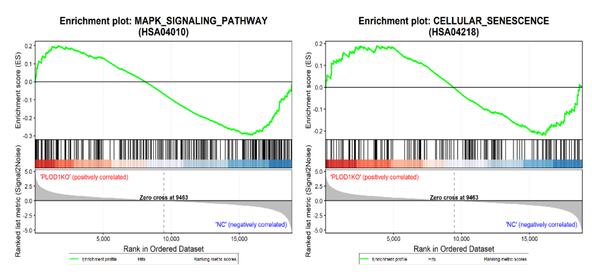


Fig.9 GSEA of the MAPK signaling pathway and cellular senescence pathway between PLOD1 KO and NC groups.

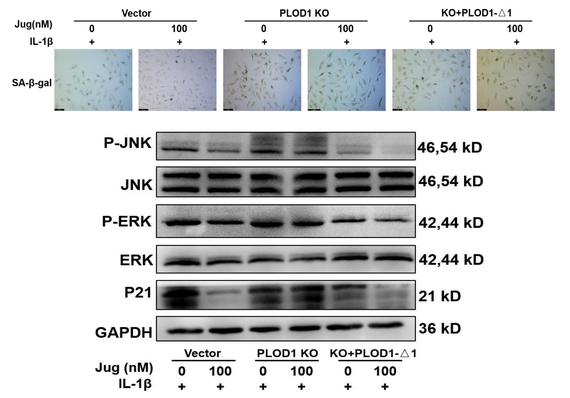


Fig.10 SA-β-gal staining and Western blot analysis on senescence associated pathway.

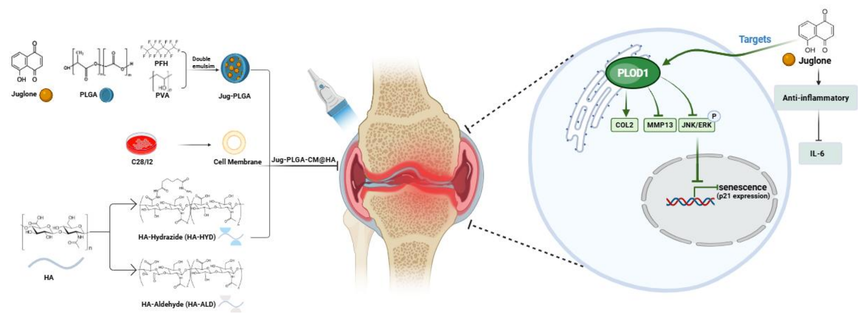


Fig.11 Molecular mechanism diagram of Juglone targeting PLOD1 to regulate the MAPK signaling pathway for inhibiting cellular senescence in the treatment of OA in chondrocytes.

References
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