# Novel Role of lncRNA H19 in Osteoarthritis Subchondral Bone Remodeling and Treatment

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INTRODUCTION: Emerging evidence suggests that aberrant subchondral bone remodeling upon excessive mechanical loading might play important role in the onset of osteoarthritis (OA). A long non-coding RNA (lncRNA) H19 was reported to be associated with OA progression and regulate mechano-transduction at cellular level, however, its role in OA subchondral bone has not been reported. This study aimed to examine the relationship between H19 and OA subchondral bone remodeling, and to develop a novel strategy for OA treatment via targeting H19.

METHODS: Human subchondral bones were collected from patients with knee OA undergoing joint replacement surgery. Wild-type C57BL/6 mice and same genetic background transgenic mice with osteocyte-specific deletion of H19 (cKO) mice were used, and OA phenotype was induced by destabilization of the medial meniscus (DMM) surgery. To verify the effect of mechanical stimulation on osteocytes, MLO-Y4 cells were subjected to unidirectional fluid shear stress (FSS) followed by RNA sequencing analysis. We developed a specific gene-delivery system by combining Fe3O4 nanoparticles and metal-organic frameworks (MOFs) to form a magnetic MOFs (MMOFs) for the delivery of anti-H19 antisense oligonucleotides (ASOs) to the target site in the presence of external magnetic field.

RESULTS SECTION: Human subchondral bone of end-stage OA had higher level of H19, which was associated with increased bone mass and more H19 expressing osteocytes. In wild-type mice, DMM surgery led to cartilage damage, subchondral sclerosis, and increased H19 expression in subchondral bone. On the contrary, cKO mice with H19 ablation were much less vulnerable to DMM induced OA phenotypic changes. In MLO-Y4 cells, H19 induced PI3K/AKT/GSK signaling activation and mediated osteocyte mechano-response upon FSS stimulation. Finally, MMOFs were successfully synthesized, and shown as an efficient delivery system with satisfactory distribution to the target site and effectiveness in terms of down-regulating H19 expression, which remarkably alleviated subchondral bone remodeling and OA phenotype.

DISCUSSION: Our results provide new evidence that elevated H19 expression in osteocytes could contribute to the aberrant subchondral bone remodeling and subsequently cartilage damage in OA development. H19 appears to be required for osteocyte response to mechanical stimulation, and targeting H19 represents a promising new approach for OA treatment.

SIGNIFICANCE/CLINICAL RELEVANCE: Targeting osteocyte H19 or subchondral bone shed light on the development of novel strategies for OA treatment.

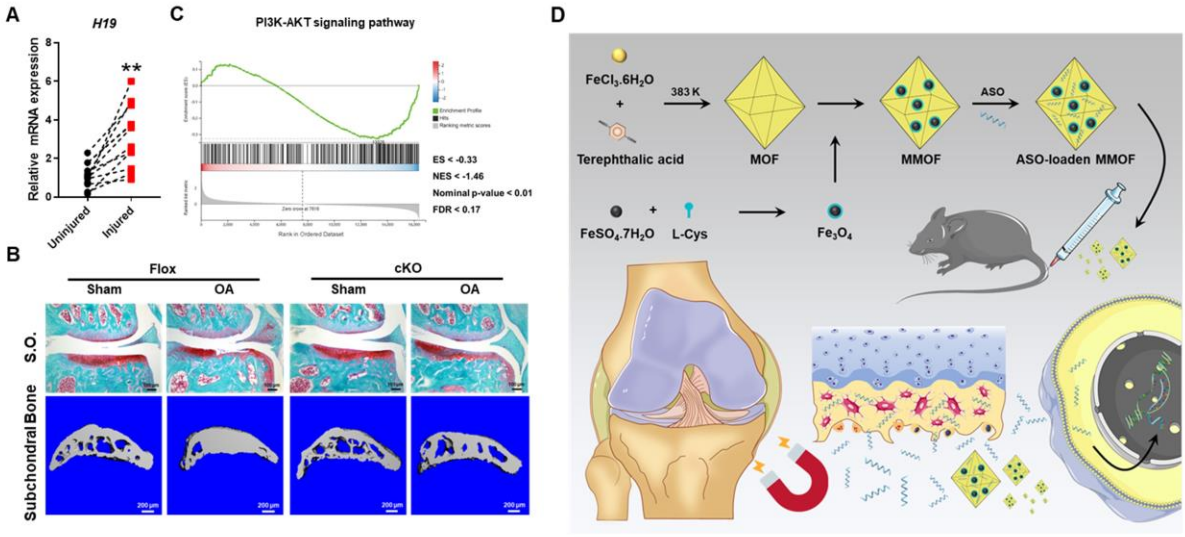


**Figure 1.** (A) The RNA expression of H19 in human bone samples through qPCR analysis. N=12 for each group. (B) Safranin-O/fast green of knee joint sections and 3D reconstruction of subchondral bone from Flox and cKO mice after DMM surgery. (C) GSEA showing the enrichment of PI3K-AKT signaling pathways in MLO-Y4 cells transfected with control and ASO after FSS stimulation. n = 4 per group. (D) Schematic illustration showed MMOF targeted on H19 inhibition in subchondral bone representing a novel and effective approach for OA treatment. *P < 0.05, **P < 0.01, Results are expressed as mean ± standard deviation (s.d.).