AAV2-FGF18 gene therapy protects against cartilage loss and subchondral bone in a mechanically induced model of osteoarthritis

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INTRODUCTION: Osteoarthritis (OA) is a highly debilitating, degenerative pathology of cartilagenous joints affecting over half a billion people around the world. The total global economic burden of OA is estimated at $260-519 billion and growing, driven mainly by aging global population and increasing rates of obesity. To date, only a treatment regimen of a series of intra-articular injections of a Fibroblast Growth Factor 18 (FGF18) analog has demonstrated clinically meaningful chondroanabolic effects in placebo-controlled human trials. Despite this, the treatment remains limited by the requirement for up to 12 injections per year in bilateral knee OA, which may need to be sustained indefinitely to prevent reversal of efficacy. Our work focuses on the development of a novel single injection disease-modifying gene therapy, based on FGF18's chondroanabolic activity.

METHODS: OA was induced in adult male Sprague-Dawley rats using destabilization of the medial meniscus (DMM) for 3 weeks, followed by intra-articular treatment with 3 dose levels of AAV2-FGF18 ($1x10^{10}$, $1x10^{11}$, $5x10^{11}$ vg), rhFGF18 protein (5 µg), and PBS (50 µL). Durability, redosability, and biodistribution were measured by quantifying nLuc reporter bioluminescence. Transcriptomic analysis was performed by RNA-seq on primary human chondrocytes in culture and rat knee joints. Morphological analysis was performed on sagittal sections of whole knee joints stained with Safranin O/Fast Green and anti-PRG antibody. Statistical analysis included the Anderson-Darling normality test, Multiple Analysis of Variance, Tukey's Honestly Significant Difference Post-Hoc test, and Chi-Squared Test for Multiple proportions (p_{Crit}=0.05, $p_{Crit,DESeq2}$=0.01).

RESULTS SECTION: Dose-dependent reductions in cartilage defect size were observed in the AAV2-FGF18-treated joints relative to the vehicle control (PBS). Total defect width (Fig. A) was reduced by up to 76% and cartilage thickness in the thinnest zone (Fig. B) was increased by up to 106% relative to PBS. Morphologically, the vehicle-treated joints exhibited pronounced degeneration, ranging from severe cartilage erosion and bone void formation, to subchondral bone remodeling (Fig. C) and near-complete subchondral bone collapse. In contrast, AAV2-FGF18-treated joints appeared significantly more anatomically normal, with only regional glycosaminoglycan loss and marginal cartilage erosion. While effective at reducing cartilage lesions, treatment with repeat rhFGF18 injections resulted in significant joint swelling (19% increase in diameter), as well as a decrease in PRG4 staining uniformity and intensity. In contrast to early-timepoint in vitro RNA-seq analysis, which showed a high degree of concordance between protein- and gene therapy-treated chondrocytes, in vivo transcriptomic analysis, 3 weeks post-final dosing, revealed few gene expression changes following protein treatment. On the other hand, the gene therapy treatment exhibited a high degree of durability and localization over the study period in both healthy and OA joints, upregulating several chondroanabolic genes while downregulating OA- and fibrocartilage-associated markers.

DISCUSSION: FGF18 gene therapy treatment of OA joints can provide benefits to both cartilage and subchondral bone, with a high degree of localization and durability. In contrast to repeated rhFGF18 protein injections, the gene therapy is not limited by joint pharmacokinetics and possesses a superior safety and efficacy profile. In conclusion, a single injection of AAV2-FGF18 gene therapy reduces cartilage loss and subchondral bone damage in a model of mechanically induced osteoarthritis.

SIGNIFICANCE: Protection of cartilage and subchondral bone following a single injection of AAV2-FGF18 in a mechanically induced model of OA, which has previously translated to clinical efficacy of the repeat protein injection treatment, sets an important foundation for the advancement of AAV2-FGF18 to human clinical studies.

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IMAGES AND TABLES: