

BMP-2 GENE TRANSFER ALTERS COURSE OF DISC DEGENERATION IN RABBIT MODEL

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INTRODUCTION: The concept of intradiscal gene therapy for the treatment of intervertebral disc degeneration has been extant since the late 1990s [1,2]. However, efficacy of gene transfer in altering the course of degeneration in a reproducible animal model of disc degeneration previously has not been established. In the current study, we injected degenerating rabbit discs with adenoviral vectors carrying the human BMP-2 gene to assess efficacy in terms of MRI and x-ray outcome measures.

METHODS: Intervertebral disc degeneration was induced in 13 skeletally mature female NZW rabbits by anterolateral stab of the L2-3, L3-4, and L4-5 lumbar discs by a 16-ga. needle to a depth of 5 mm. Discs L1-2 and L5-6 were maintained as intact controls. Three weeks post-stab, saline—with or without virus—was injected directly into the three stabbed lumbar discs of each rabbit with a 30-ga. needle. Group 1 (n=8) received the adenovirus construct Ad/hBMP-2 containing the therapeutic human BMP-2-encoding gene. Group 2 (n=5) received saline only. The rabbits were followed longitudinally with midsagittal T2-weighted MRIs preoperatively, and 3, 6, and 12 weeks post-stab. Degeneration was assessed at each time point by MRI Index (product of nucleus pulposus area and signal intensity). Plain x-rays were taken at week 12 to assess for osteophyte formation and possible fusion. Nucleus pulposus was harvested at 6 weeks post-stab from 5 animals (3 rabbits from Ad/hBMP-2 treatment group, and 2 rabbits from saline control group), cultured whole in serumless media for 48 hours, and supernatant analyzed by ELISA to measure hBMP-2 production (normalized to wet weight of harvested nucleus pulposus tissue).

RESULTS: MRI: Saline injection alone at 3 weeks failed to prevent significant decreases ($p < .05$) in MRI Index by 6 and 12 weeks post-stab. In contrast, discs injected with Ad/hBMP-2 at 3 weeks exhibited less decrease in MRI Index than the saline controls. By 12 weeks, the saline-injected discs had lost approx. 49%

of their MRI Index, in contrast to only a 25% decrease in the Ad/hBMP-2 treated discs. Plain x-ray: Lateral and anterior-posterior plain films demonstrated no obvious bony intervertebral fusion in either the saline control or the Ad/hBMP-2 treated discs. There also was no discernable difference in osteophyte formation, disc height, or endplate sclerosis between the two groups. ELISA: BMP-2 levels detected by ELISA at 6 weeks post-stab were 72 ± 47 (pg/ml/mg) in the intact control discs, 34 ± 11 in the saline injected controls, and 217 ± 124 in the Ad/hBMP-2 injected discs. These data demonstrate that vigorous transgene expression was obtained in degenerating discs 3 weeks after their injection with Ad/hBMP-2.

DISCUSSION & CONCLUSIONS: The results of this study suggest that gene transfer of a growth factor encoding sequence, hBMP-2, can delay disease progression in an animal model of intervertebral disc degeneration, as assessed by clinically relevant T2-weighted MRIs. The mechanisms of therapeutic effect likely include sustained BMP-2 transgene expression as well as proteoglycan synthesis upregulation and increased disc water content. Direct adenovirus-mediated transfer of the hBMP-2 gene did not result in bony fusion in this rabbit model of intervertebral disc degeneration by 12 weeks. This study, to our knowledge, is the first demonstration of efficacy of gene transfer in favorably altering the course of degeneration in a reproducible animal model of disc degeneration.

REFERENCES:

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