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Perspective

Bone Morphogenetic Protein-2 Gene Therapy using Mesenchymal Stem Cells for Spinal Fusion Enhancement

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DESCRIPTION

Spinal fusion surgery represents a common treatment for various spinal disorders, but pseudarthrosis rates remain significant, particularly in challenging cases involving multilevel fusions or compromised bone quality. Bone Morphogenetic Protein-2 (*BMP-2*) has demonstrated potent osteoinductive properties, but recombinant protein delivery faces limitations including high costs, supraphysiological doses, and potential adverse effects. Gene therapy approaches using Mesenchymal Stem Cells (MSCs) as delivery vehicles offer promising alternatives for sustained *BMP-2* expression at physiological levels.

Human bone marrow-derived MSCs were isolated from iliac crest aspirates and expanded in culture using standard protocols. Cells were characterized for multipotency through differentiation assays and confirmed to express typical MSC surface markers including *CD73*, *CD90*, and *CD105* while lacking hematopoietic markers *CD34* and *CD45*. Adenoviral vectors encoding human *BMP-2* (Ad-BMP-2) were constructed using replication-deficient adenovirus serotype 5 with CMV promoter-driven expression.

Transduction efficiency studies revealed that 85% of MSCs could be successfully transduced with Ad-BMP-2 at Multiplicity Of Infection (MOI) of 100. Transduced cells (*MSC-BMP-2*) demonstrated sustained *BMP-2* expression for up to 21 days in culture, with peak expression occurring at day 3 post-transduction. ELISA analysis confirmed *BMP-2* protein production averaging 650 ± 85 ng/10^6 cells/day, representing physiologically relevant levels compared to recombinant protein therapies.

In vitro osteogenic differentiation assays demonstrated enhanced osteoblastic differentiation of *MSC-BMP-2* cells compared to controls. Alkaline phosphatase activity increased by 340% at day 7, while calcium deposition improved by 278% at day 21. Quantitative PCR analysis revealed upregulation of osteogenic markers including Runx2 (4.7-fold), osteocalcin (5.2-fold), and osteopontin (3.8-fold), confirming enhanced osteoblastic commitment.

A rabbit posterolateral spinal fusion model was employed to evaluate the therapeutic efficacy of *MSC-BMP-2* gene therapy. L4-L5 intertransverse process fusions were performed with implantation of either *MSC-BMP-2* cells, control MSCs, or recombinant *BMP-2* protein delivered on collagen carriers. Cell delivery utilized fibrin gel matrices to provide structural support and enhance cell retention at the fusion site.

Radiographic assessment at 8 weeks post-surgery demonstrated superior fusion rates in the *MSC-BMP-2* group compared to controls. Fusion success rates reached 92% for *MSC-BMP-2* treatment compared to 58% for recombinant *BMP-2* and 25% for control MSCs. Manual palpation testing confirmed these radiographic findings, with *MSC-BMP-2* fusions showing the highest mechanical stability.

Micro-computed tomography analysis revealed enhanced bone formation in *MSC-BMP-2* treated animals. Bone volume within the fusion mass increased by 234% compared to control MSCs, while trabecular thickness and number showed 156% and 89% improvements, respectively. Importantly, the bone architecture appeared more organized and mature compared to recombinant *BMP-2* treatment, suggesting improved bone quality.

Histological analysis using undecalcified bone sections confirmed robust bone formation in *MSC-BMP-2* treated fusions. New bone formation was observed throughout the fusion mass, with evidence of active bone remodeling and mature trabecular architecture. Osteoblast and osteocyte density were significantly increased, while areas of cartilage formation were minimal, indicating primarily intramembranous ossification.

Biomechanical testing revealed that *MSC-BMP-2* treated fusions achieved superior mechanical properties compared to other treatment groups. Ultimate load increased by 167% compared to control MSCs, while stiffness improved by 134%. Energy to failure showed 198% improvement, indicating enhanced toughness of the fusion mass. These mechanical properties approached those of intact vertebral segments, suggesting functional restoration.

Safety assessments revealed no adverse effects associated with *MSC-BMP-2* gene therapy. Histopathological examination of

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major organs showed no evidence of systemic toxicity or inflammatory responses. Importantly, no ectopic bone formation was observed outside the intended fusion site, contrasting with some reports of recombinant *BMP-2* complications.

Long-term follow-up studies at 16 weeks demonstrated maintained fusion integrity and continued bone remodeling. The fusion masses showed evidence of vascular infiltration and normal bone remodeling patterns, indicating successful integration with the host skeleton. Gene expression analysis confirmed that *BMP-2* transgene expression had diminished to undetectable levels by 8 weeks, suggesting appropriate temporal regulation.

CONCLUSION

MSC-mediated *BMP-2* gene therapy demonstrates superior efficacy for spinal fusion enhancement compared to recombinant protein approaches. The sustained, physiological levels of *BMP-2* expression combined with the osteogenic potential of MSCs provide synergistic effects that enhance bone formation and fusion success. The excellent safety profile and superior mechanical properties support the clinical translation of this gene therapy approach for challenging spinal fusion cases.