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Effect of Osteoactivin and Bone Morphogenetic Protein-2 on soft tissue in Rat Spinal Fusion Model

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Title: Effect of Osteoactivin and Bone Morphogenetic Protein-2 on soft tissue in Rat Spinal Fusion Model

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Executive Summary

Osteoinductive therapeutic strategies are essential for the bone healing process and are applicable in multiple orthopaedic procedures. The novel protein Osteoactivin (OA) has proven to stimulate osteoblast differentiation and function in vitro and bone regeneration in vivo in the rat model. More recently, OA has shown significant bone regeneration ability in sheep. The goal of this study is the comparison of osteoactivin with bone morphogenetic protein-2 (BMP-2) in the rat spinal fusion model. Abdelmagid et al. ¹ have shown that OA acts downstream of BMP-2. Additionally, a positive correlation was found between OA mRNA expression and protein production in response to treatment with BMP-2. Elimination of OA expression through the use of antisense OA oligonucleotides in the osteoblast cultures of BMP-2 treated groups resulted in osteoblast differentiation similar to that of the control group. This demonstrates that BMP-2 has limited osteoinductive potential without the downstream protein, OA. If OA expression ceases, osteoblast differentiation and osteoinductive ability is reduced (to levels similar of the control group). These findings indicate that OA could function as an osteoblast-specific component of the BMP-2 cascade. This specificity is especially significant as targeting of OA in the BMP-2 cascade could prevent harmful side effects of general BMP-2 activation including nerve root injury, carcinogenesis, retrograde ejaculation and postoperative radiculitis. ²⁻⁶ Autologous bone grafting was also utilized in this study to determine its effect on bone regeneration for OA and BMP-2. Autologous bone grafting is of limited value in pediatric and geriatric populations due to an increased risk of complications and limited amount of useable

bone.⁷ Additional disadvantages with autologous bone grafting include the development of complications such as infection, hematoma, and fracture in 19% of patients that undergo iliac crest bone graft harvesting and 6% of patients that undergo reamer/irrigator/aspirator (RIA) harvest.⁷ Comparison of the osteoinductive ability of OA and BMP-2 with and without autologous bone graft in rat spinal fusion occurred through the utilization of 70 male Sprague-Dawley rats. No study has previously compared OA and BMP2 in the spinal fusion model.

Following the study, histological analysis revealed an absence of systemic inflammation and adverse health effects in Osteoactivin and Osteoactivin with autologous bone graft treatment groups. In contrast, increased inflammation was recognized in the bone morphogenetic protein-2 treatment groups.

The aging population and the development of significant complications with bone morphogenetic protein-2 and autologous bone graft treatment compel more focused treatment options. BMP-2, an osteoinductive growth factor, has acquired an FDA listing of a warning of potential life-threatening complications.⁹ Due to the risks of current treatment options, practitioners currently utilize compounds such as BMP-2 “off label.” This designation suggests that the practitioner is utilizing the compound in a manner that is inconsistent with the purpose specified on the label by the FDA. This use can be harmful to patient and practitioner alike. If OA can continue to be demonstrated as a viable osteoinductive compound, we will further investigate its therapeutic potential in other applicable osteogenesis surgeries and procedures. In the current situation of minimal clinically accepted osteoinductive treatments with the risk of significant adverse side effects, the performance of Osteoactivin in the stimulation of bone regeneration is important for the potential development of an improved therapeutic for osteoporotic patients and procedures requiring the use of osteogenesis. Clinical trials are the next step for Osteoactivin.

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