BONE HEALING INDUCED BY ADENOVIRAL BASED GENE THERAPY WITH BMP-2 AND TGF BETA

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Intoduction: Bone grafting, the currently accepted treatment for severe bone defects is a traumatizing procedure, causing disturbances of microcirculation and generally requiring months of immobilisation and discomfort. Locally acting cytokines like BMPs or TGFs have been shown recently to enhance physiological bone healing efficiently. Our study explores the potential of adenoviral gene therapy with BMP-2 and TGFβ as a more efficient approach to accelerate bone healing in complex bone defects.

Methods: A long bone segmental defect model in the femur of mature New Zealand White rabbits was used in all experiments. The periosteum layer was removed completely 1 cm proximal and distal to the gap. The segmental defect was then stabilized by internal fixation using a 7 hole DCP-plate. A chamber was formed by closing the muscle layers completely around the 1.3 cm gap. Viral vectors encoding BMP-2 (Ad-BMP-2), TGFβ (Ad-TGFβ), or luciferase (Ad-luc) were diluted with sterile saline solution and injected directly into the gap at a concentration of $7x10^{10}$ particles. In order to evaluate the therapeutic effect of the vectors, ossification and bone healing were followed radiographically. 16 weeks postoperatively, the rabbits were sacrificed and analyzed by histomorphometry. The results were compared with those of the control rabbits. The animal trial was approved by the Institutional Animal Care and Use Committee of the University of Pittsburgh.

Results: The results of the radiographic follow-up showed a bony union of the segmental defect in all 6 rabbits, 13 weeks after treatment with Ad-BMP-2, compared to non-unions in the control group (4 rabbits). The biomechanical testings using Instron will be presented. Radiographically, the treatment with Ad-TGFβ lead to an increase of ossification at the site of injection, a complete bony union was gained in 4 out of 5 rabbits 16 weeks postoperatively. The analysis of histomorphometry demonstrated that a treatment with Ad-TGFβ led to an increase of the total amount of bone in the area of interest (mean: 19.6 mm^2 vs. 9.04 mm^2), and to a doubling of the IOD (integrated optical density) (mean: 1754.8 vs.738.0).

Discussion: We demonstrate that the ossification of a long bone segmental defect model in New Zealand White rabbits can be accelerated by adenoviral transfer of growth factor genes. The transfer of the BMP-2 gene leads to complete healing in a bony union, compared to a fibrous non-union in the control group. Ad-TGFβ increases the ossification of the defect compared to the control rabbits, but a bony union resulted only in 80% of all cases. Gene therapy has the potential to circumvent the problem of fast clearence of recombinant growth factors by continuous, local synthesis of the gene product. Gene therapy with growth factors may become a new minimal invasive procedure to improve bone healing in defect fractures and to develop new, adjuvant techniques to fasten bone healing in surgery such as lumbar spinal fusions or osteosyntheses.

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