

Gene therapy for the regeneration of traumatic articular cartilage defects

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Traumatic focal defects of articular cartilage, those who penetrate the subchondral bone (osteochondral defects), heal with a repair tissue that degenerates in the course of the time. No clinically available treatment leads to complete and durable cartilage regeneration. Although the concept of gene therapy for cartilage damage appears elegant, current research indicates that an adaptation of gene transfer techniques to the problem of a circumscribed cartilage defect is required in order to successfully implement this approach. In particular, the localized delivery into the defect of therapeutic gene constructs is desirable. Current strategies aim at inducing chondrogenic pathways in the repair tissue that fills such defects. Among the most studied candidates, polypeptide growth factors have shown promise to enhance the structural quality of the repair tissue. Our group investigates the regulation of chondrogenesis in cartilage defects. We evaluated different therapeutic candidates in two- and three-dimensional systems of chondrogenesis *in vitro*. Using an osteochondral defect model in the rabbit knee we showed that nonviral overexpression of a human insulin-like growth factor I (IGF-I) and fibroblast growth factor 2 (FGF-2) cDNA by transplanted articular chondrocytes encapsulated in alginate spheres improved articular cartilage repair and accelerated the formation of the subchondral bone compared to control implants. In addition, the direct application of recombinant adeno-associated virus (rAAV) vectors to sites of cartilage damage allows for efficient and sustained transgene expression. We could further demonstrate

that rAAV-mediated overexpression of FGF-2 is sufficient to significantly improve the overall repair, filling, architecture, and cell morphology of osteochondral defects in rabbit knee joints. These data demonstrate that implantation of transfected articular chondrocytes encapsulated in alginate spheres into deep articular cartilage defects augments cartilage defect repair *in vivo* via stimulation of chondrogenesis. The data also provide a basis for rAAV application to sites of articular cartilage damage to deliver therapeutic agents that promote cartilage repair. These results suggest that therapeutic growth factor gene delivery using either encapsulated and transplanted genetically modified chondrocytes or direct rAAV gene vectors may be applicable to sites of focal articular cartilage damage. A better understanding of the basic scientific aspects of cartilage defect repair, together with the identification of additional molecular targets and the development of improved gene-delivery techniques, may allow a clinical translation of gene therapy for cartilage defects.

REFERENCES

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ACKNOWLEDGEMENTS: This research work is supported by a grant from the AO Foundation (Davos, Switzerland) through the Biotechnology Advisory Board and by the Deutsche Forschungsgemeinschaft (DFG MA 2363/1-1 and/1-2 to HM and CU 55/1-1 and/1-2 to MC and HM).