Cartilage Regeneration in an Immunocompromised Rat Critical-Size Xiphoid Cartilage Defect Model

Y. Wang[1], L. Xie[1], H.R. Moyer[2], A. Nizkorodov[1], S. Hyzy[1], Y. Huang[3], K. Truncale[3], R.E. Guldberg[1], Z. Schwartz[1], B.D. Boyan[1]

[1] Institute for Bioengineering and Bioscience, Georgia Institute of Technology, Atlanta, GA, USA; [2]Emory University Medical School, Division of Plastic and Reconstructive Surgery, Atlanta, GA, USA; and [3]Musculoskeletal Transplant Foundation, Edison, NJ, USA

Introduction: Large cartilage defects resulting from osteoarthritis, trauma and surgical excision are common clinical problems. Surgical efforts to repair cartilage defects have focused on delivering cells or engineered cartilage implants into the lesions. Current models examine osteochondral repair, although many cartilage defects do not extend to the subchondral tissue. In this study, we established a critical size defect in the nude rat xiphoid and validated its ability to discriminate among cartilage repair strategies.

Methods: Defects were created in the xiphoid cartilages of 8-week-old athymic rats using dermal biopsy punches varying from 1-4 mm in diameter. This produced a cylindrical, full-thickness defect in the center of the xiphoid. The critical size of the xiphoid defect was evaluated based on EPIC-μCT, radiographic and histological analysis 35-days post surgery (8 rats/treatment group). Eight different cartilage substitutes composed of demineralized bone scaffolds, cartilage particles (CP) or heat-inactivated cartilage particles (ICP), and different doses of a bioactive peptide were transplanted into 3mm xiphoid defects. Empty defects served as controls. 28 days after surgery, the xiphoid defects were harvested and subjected to evaluation using EPIC-μCT, X-ray, and safranin-O/fast green staining.

Results: At harvest, 1-mm defects were completely infiltrated with cartilage matrix (Fig 1), despite a small translucent area seen on X-ray. 2-mm defects contained high proteoglycan content cartilaginous tissue, based on micro-CT analysis, and less than 1mm^3 area remained unhealed. Both 3-mm and 4-mm defects failed to heal and exhibited low proteoglycan content in the center of defect. Therefore, the 3-mm defect was chosen as the critical-size non-articular cartilage defect model.

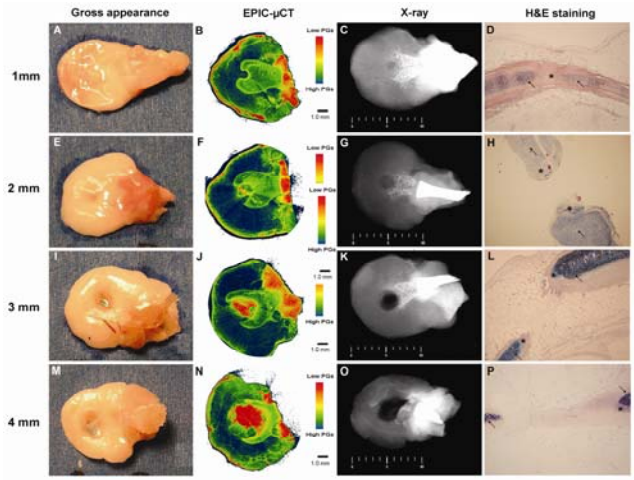

Fig. 1 Xiphoid cartilage defects varied from 1mm to 4mm 35-days post surgery.

Scaffolds with or without cartilage particles filled the defect sites but did not result in neo-cartilage formation (Fig. 2II, IV, VIII). Incorporation of the peptide into the scaffolds significantly promoted the synthesis of neo-cartilage close to the edge of the defect (Fig. 2III, $P<0.05$ vs. group I). Active cartilage particles plus peptide induced not only dose-dependent increases in the formation of neo-cartilage, but also homogenous distribution throughout the defects (Fig. 2V-VII, $P<0.05$ vs. group III). These effects were less pronounced when the heat-inactive cartilage particles were used (Fig. 2IX, $P<0.05$ vs. group VII).

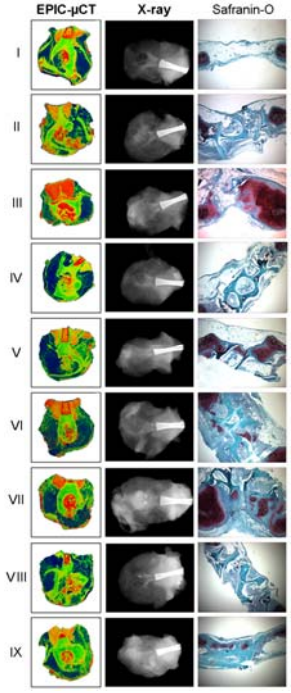

Fig. 2 Repair of xiphoid defect by different cartilage substitutes 28-days after surgery.

Conclusions: Our critical-size xiphoid cartilage defect model is a non-articular, non-weight bearing chondral defect model, which provides an economic, feasible, and reproductive approach to screen engineered cartilage in terms of critical-size cartilage repair and cartilage regeneration. Cartilage substitutes differentially integrated with native tissue and healed the defects. The peptide increased synthesis of neo-cartilage in a dose-dependent manner. Active cartilage particles appeared to provide homogeneous distribution of growth factor through the scaffolds, potentially exerting synergetic effects with peptides on the regeneration of cartilage.

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