Validating the subcutaneous model of injectable autologous cartilage using a fibrin glue scaffold.

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Abstract:

PURPOSE: To create and validate an injectable model for autologous in vivo cartilage engineering with ultimate clinical applicability in human subjects.

HYPOTHESIS: Cartilage can be generated subcutaneously using fibrin glue and autologous chondrocyte components.

BACKGROUND: To date, cartilage engineering studies have been limited by several factors. Immunocompromised animals and nonautologous chondrocytes have been successfully used to create cartilage, but results using identical designs failed in immunocompetent subjects. Recent studies using more biocompatible tissues and matrices have been performed with both in vitro and in vivo steps. Although successful, several problems are notable. In vitro cartilage displays a poor modulus of elasticity, even after in vivo implantation. Variable deformation and volume loss occurs when in vitro specimens are matured in vivo. These concerns limit the clinical utility of these methods. We therefore set out to create autologous cartilage using a model that was clinically feasible, easy to create, and could be performed with very low patient harvest morbidity.

MATERIALS AND METHODS: Eight New Zealand white rabbits underwent a unilateral harvest of ear cartilage. Samples were then digested using standard methods. Cell counts and survival assays were performed before implantation. One sample of fibrin glue (Tisseel) and chondrocytes was

injected subcutaneously into each donor rabbit and then left in situ for 3 months. A second sample with both basic fibroblast growth factor (b-FGF) and insulin-like growth factor (IGF)-1 in the injection suspension was also assessed (for a total of 16 samples). After harvest, analysis of overall volume, histology, and chondrocyte drop out counts was performed.

RESULTS: Cartilage formation occurred in 8 of 14 (57%) specimens that were obtained at the time of sacrifice. Of note, 6 of 7 (85%) non-growth-factor containing samples yielded positive results. Comparison with the success rate using concomitant growth factors (2/7) showed a negative effect on cartilage yield (P = .015). Chondrocyte survival, based on chondrocyte dropout counts, was not effected. Angiogenesis appeared to correlate with cartilage formation in the central regions of the implant. Alcian blue demonstrated the presence of active matrix deposition, and elastin Verhoff-van Geison (EVG) stains were positive, showing an elastic cartilage phenotype. Very limited osteoid formation was seen in successful implants. Failed implants demonstrated avascular necrosis, giant cell reactions, and inflammatory infiltrates.

CONCLUSIONS: This study validates the subcutaneous site as a recipient bed for the engineering of autologous cartilage in vivo. It also represents the first subcutaneous implantation of fibrin glue and chondrocytes in an immunocompetent host as well as the first published report of elastic cartilage generation in vivo. Although the model needs to be further streamlined to increase yields and overall volume, this study clearly demonstrates the feasibility of in vivo chondrogenesis (85% success). The addition of FGF and IGF-1 at the concentrations used negatively influenced cartilage yield. However, extrapolation of these results to other combinations or concentrations can not be done, and this issue deserves further investigation.