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Abstract:

Improved methods of bone regeneration are needed in the craniofacial rehabilitation of patients with significant bone deficits secondary to tumor resection, congenital deformities, and prior to prosthetic dental reconstruction. In this study, a gene-enhanced tissue-engineering approach was used to assess bone regenerative capacity of Sonic hedgehog (Shh)-transduced gingival fibroblasts, mesenchymal stem cells, and fat-derived cells delivered to rabbit cranial bone defects in an alginate/collagen matrix. Human Shh cDNA isolated from fetal lung tissue was cloned into the replication-incompetent retroviral expression vector LNCX, in which the murine leukemia virus retroviral LTR drives expression of the neomycin-resistance gene. The rat beta-actin enhancer/promoter complex was engineered to drive expression of Shh. Reverse transcriptase-polymerase chain reaction analysis demonstrated that the transduced primary rabbit cell populations expressed Shh RNA. Shh protein secretion was confirmed by enzyme-linked immunosorbent assay (ELISA). Alginate/ type I collagen constructs containing 2 times 106 Shh-transduced cells were introduced into male New Zealand White rabbit calvarial defects (8 mm). A total of eight groups (N=6) were examined: unrestored empty defects, matrix alone, matrix plus the three cell populations transduced with both control and Shh expression vectors. The bone regenerative capacity of Shh

gene enhanced cells was assessed grossly, radiographically and histologically at 6 and 12 weeks postimplantation. After 6 weeks, new full thickness bone was seen emanating directly from the alginate/collagen matrix in the Shh-transduced groups. Quantitative two-dimensional digital analysis of histological sections confirmed statistically significant ($P<0.05$) amounts of bone regeneration in all three Shh-enhanced groups compared to controls. Necropsy failed to demonstrate any evidence of treatment-related side effects. This is the first study to demonstrate that Shh delivery to bone defects, in this case through a novel gene-enhanced tissue-engineering approach, results in significant bone regeneration. This encourages further development of the Shh gene-enhanced tissue-engineering approach for bone regeneration.

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