Introduction: Adenoviral vectors represent one of the major delivery methods being researched to introduce genes into mammalian cells. Attempts at achieving a clinically useful gene therapy have been disappointing because of transient expression of the gene of interest. However, in some clinical situations such as fracture non-unions and the treatment of other bone defects, transient expression of the exogenous gene may be all that is required. It has been shown that rat bone marrow cells infected with an adenoviral vector containing BMP2 can be used to induce bone healing in a rat femoral defect model. A concern with using an adenovirus for gene therapy has been with systemic toxicity and with the possibility of depositing adenovirus in other areas of the body. The purpose of this study was to compare the tissue distribution of recombinant adenovirus when either an ex vivo or an in vivo gene transfer strategy was used to treat femoral defects in rats. Therefore, the tissue distribution of recombinant adenovirus containing the BMP-2 cDNA was determined after either implantation of BMP-2 producing cells into the femoral defect(ex vivo) or direct injection of the adenovirus into the defect site (in vivo).

Methods: All procedures involving animals were approved by our institution’s Animal Welfare Committee which follows the NIH policy on the humane care and use of laboratory animals.

Results: A PCR product was detected 24 and 48 hours after injection but not at 1 week or 2 weeks. No signal was detected in any organ outside of the implant site at any time point with this ex vivo gene therapy technique.

Discussion: Adenovirus gene therapy strategies show great potential for use in humans to treat problems associated with bone loss. However, before this gene therapy can be used clinically, certain questions about the safety of the recombinant adenovirus must be answered. Therefore, we examined the time course and tissue distribution of recombinant adenovirus after implantation of adenovirus infected bone marrow cells and after direct injection of adenovirus into the bone defect site. In our previous study, no obvious immunogenic response was noted in the rats treated with the adenovirus infected bone marrow cells. The adenovirus infected bone marrow cells appear to remain locally at the defect site. Signal within the limits detected by quantitative PCR was not noted in any other organ. In contrast, when adenovirus was directly injected at the defect site, it spread systemically to the lung and liver. The transient presence of the adenovirus in these tissues may be due to clearance by innate immune mechanisms (Worgall et al, 1997). Another possible explanation for this is the low number of infected cells (5*10^6) that is required to heal the bone defect. Other adenovirus based gene therapies have used adenovirus at orders of magnitude greater doses. These results are encouraging with regard to the safety of this adenovirus based gene therapy and suggest that this gene therapy can be safely adapted for use in humans.


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