Introduction: Cartilage homeostasis relies on a balance between anabolic growth factors such as IGF-I and catabolic agents particularly IL-1. Catabolism predominates in disease conditions such as synovitis and osteoarthritis. From a therapeutic standpoint, IGF-I promotes cartilage healing when administered intra-articularly, but the residence time is limited to several days. Delivery of IGF-I by gene transduction of the synovial structures would be a less invasive and more persistent means of supplying growth factors. Abrogation of the catabolic axis through antagonism of IL-1 action would further add to the restoration of cartilage integrity, and combination of IL-1 receptor antagonist protein (IL-1ra) and IGF-I in the same gene construct, or given concurrently in stand-alone gene constructs, may provide dual axis therapy that can aid in cartilage resurfacing procedures and attenuate arthritic processes. This study examined the hypothesis that co-transduction of synovial lining cells with IGF-I and IL-1ra gene constructs would increase IGF-I and IL-1ra production and aid in the restoration of depleted cartilage.

Materials and Methods: Recombinant adenoviral vectors containing the coding region of either equine IGF-I (AdIGF-I) or equine IL-1ra (AdIL-1ra) were constructed using the cre-lox system, and propagated in a 293 packaging cell line. Synovial membrane from 3 horses was digested in 0.15% collagenase and 0.015% DNAseI. Synovial monolayer cultures were established in 6-well plates expressing synoviocytes increased PG content above uninfected controls (Fig 2). In IL-1 depleted cartilage explants AdIGF-I/AdIL-1ra cotransduction of synoviocytes improved PG content in cartilage, with AdIGF-I and AdIL-1ra alone producing lesser increases in PG level (Fig 3). Matrix proteoglycan staining on toluidine stained sections reflected the PG data from cartilage (Fig 3).

Discussion: Cells of the synovial lining were readily infected with both AdIGF-I and AdIL-1ra particles. Transduced cells secreted moderate levels of IGF-I and high levels of IL-1ra. The effect of this anabolic growth factor and catabolic blocker were most apparent in restoration of PG content of damaged cartilage in AdIGF-I and AdIGF-I/AdIL-1ra co-cultures. These data suggest that combination gene therapy using growth factors that stimulate cartilage matrix synthesis and IL-1ra to block IL-1 action have partial restorative effects on cartilage PG levels. However, PG levels in AdIGF-I and AdIGF-I/AdIL-1ra combination therapy were similar, indicating the need for IL-1ra presence at the time of the IL-1 flux to prevent PG depletion, rather than after IL-1 actions had started.


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