Application of a disease-regulated promoter is a safer mode of local IL-4 gene therapy for arthritis

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The application of disease-regulated promoters in local gene therapy for rheumatoid arthritis potentiates the development of a sophisticated treatment that relies on a restricted and fine-tuned supply of biologicals. Although several studies have investigated regulated promoters for achieving effective transgene expression during arthritis, none have explored their potential for minimizing deleterious effects arising from constitutive overexpression of transgenes under naive conditions. Using naive and collagen-induced arthritic mice, we examined the applicability of a hybrid interleukin-1 enhancer/interleukin-6 proximal promoter for achieving efficacious murine interleukin-4 gene therapy under arthritic conditions, while minimizing interleukin-4-induced inflammation under naive conditions. We found strong upregulation of transgene expression in virally transduced knee joints under arthritic conditions compared to levels in naive animals. Besides its responsiveness, the promoter strength proved sufficient for generating therapeutically efficacious levels interleukin-4, as demonstrated by the successful protection against cartilage erosion in collagen-induced arthritis. Most importantly, promoter-mediated restriction of the potent chemotactic interleukin-4 in naive animals strongly reduced the amounts of inflammatory cell influx. This study suggests the suitability of the interleukin-1 enhancer/interleukin-6 proximal promoter for the development of a local gene therapy strategy for rheumatoid arthritis that requires fine-tuned and restricted expression of transgenes with a pleiotrophic nature.

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