Comparison of IL-10 and MCP-1-7ND gene transfer with AAV9 vectors for protection from murine autoimmune myocarditis.

Abstract:
Overexpression of therapeutic genes with potential disease-limiting effects, specifically at the site of inflammation, remains a major clinical challenge. In this study, we investigate the potential of adeno-associated virus (AAV)-9-mediated cardiac expression of the anti-inflammatory mediators interleukin (IL)-10 and a dominant-negative inhibitor of monocyte chemoattractant protein-1 (MCP1-7ND) on prevention of autoimmune myocarditis. Autoimmune myocarditis was induced by immunizing A/J mice with subcutaneous injection of 120 µg cardiac troponin I (cTnI) on Days 0, 7, and 14. Two weeks prior to initial immunization, each mouse received a single systemic dose of 10(12) AAV9 vectors carrying the coding sequence of IL-10 or MCP1-7ND transcriptionally targeted to the heart. Mice were sacrificed 28 days after initial immunization for further analysis. Only expression of IL-10 resulted in a highly significant decrease in myocardial inflammation and fibrosis, as well as an increased ejection fraction compared with controls. Further analyses of cytokine profiles of cTnI-stimulated splenocytes from IL-10 and MCP1-7ND-treated mice revealed significant alterations compared with controls. In addition, transcript levels of chemokine receptor CCR4 and T-cell activation gene were significantly reduced in hearts of
IL-10-treated mice as determined by quantitative real-time PCR. Our study suggests that cardiac expression of IL-10 with AAV9 vectors is a promising therapeutic approach for autoimmune myocarditis.