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Cytokine therapy for proteoglycan-induced arthritis

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Keywords

Aggregan, arthritis, IFN-?, IL-4, IL-10, proteoglycan

Context

The destructive inflammation in the rheumatoid synovium is associated with a dominant Th1-type immune response. A propensity to develop a vigorous Th1-type response may predispose an individual to severe rheumatoid arthritis. BALB/c mice are an inbred strain which display a propensity for dominant Th2 responses. These mice develop only mild arthritis following challenge with *Borrelia burgdorferi*. However, immunisation of BALB/c mice with human cartilage proteoglycan (PG) is known to induce a $CD4^+$ T cell mediated progressive polyarthritis and spondylitis. To examine the cytokine profile of PG-specific T cells in BALB/c mice with PG-induced arthritis and to investigate the effect of systemic Th2 cytokine administration prior to disease development and during acute arthritis.

Significant findings

A PG-specific cytokine response was evident in splenocytes after the third injection (28 days) and the ratio of increase of IFN-? production was much higher than for either IL-4 or IL-10. Mice developed arthritis approximately 1 week after the final PG immunisation. Injection of 5 ?g IL-10 daily for 21 days, starting in the pre-arthritic period (around days 52-73), resulted in a significant delay in onset and a transient reduction in severity. Administration of IL-4 or a combination of IL-4 and IL-10 totally suppressed the development of arthritis. Treatment with IL-4 starting in the pre-arthritic period also prevented any of the histological changes in the joints that were evident in the phosphate buffered saline (PBS)-treated, PG-immunised group. Measurement of cytokines produced by splenocytes in response to PG, following treatment for 21 days with IL-4, IL-10 or both, indicated that a shift from a Th1- to a Th2-type response had occurred. Levels of TNF-a, IL-6 and IFN-? transcripts in the joint were also reduced by treatment with the Th2 cytokines. When Th2 cytokine treatment was initiated at the time of peak joint swelling (approximately 2 to 4 weeks after the final PG immunisation), there was a rapid decrease in joint swelling which lasted for the duration of the treatment. However, cartilage damage was still evident histologically at the end of this period.

Comments

RA is associated with an inflammatory response with a preponderance of Th1 cytokines. Attempts to selectively divert Th1-like to Th2-like responses in the inflamed synovium form the basis of many immunotherapeutic strategies in RA. This model of PG-induced arthritis in BALB/c mice is encouraging since treatment with Th2 cytokines could both prevent disease in the pre-arthritic phase and ameliorate established arthritis, although it did not appear to reduce cartilage damage in acute disease. The efficacy of this approach in collagen-induced and streptococcal-wall-induced murine models of arthritis has been less impressive and it is possible that the genetic background of the BALB/c mice facilitates this response to Th2 cytokine treatment. Although the specificity of the Th1 cytokine responses in RA is unknown, systemic Th2 cytokine therapy may prove effective in patients. Extrapolating from this animal model, it is probable that a subset of patients with a propensity to mounting prominent Th2 responses will gain the most from this approach.

Methods

Female BALB/c mice were immunised intraperitoneally (ip) with human PG emulsified in complete Freund's adjuvant (CFA) on days 0 and 49 and PG/incomplete Freund's adjuvant on days 7 and 28. Arthritis was quantified by measuring paw thickness and histological sections were scored by a blinded histologist. The cytokine profile of splenocytes was assessed one week after each immunisation. A single-cell suspension from harvested spleens was restimulated with PG *in vitro*, and quantities of interleukin (IL)-4, interferon (IFN)-? and IL-10 were measured in the culture supernatants by ELISA. The relative quantities of cytokine mRNA in the hind paws were measured by RNase protection assay. To assess whether administration of Th2 cytokines could modify the progression of disease, 5 ?g IL-4 and IL-10, alone or in combination, were injected ip for 21 days, starting in the pre-arthritic period.

References

1. Finnegan A, Mikecz K, Tao P, Glant TT: Proteoglycan (aggrecan)-induced arthritis in BALB/c mice is a Th1-type disease regulated by Th2 cytokines. J Immunol. 2000, 163: 5383-5390.